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NORMAL ROENTGEN ANATOMY OF THE LYMPH VESSELS OF UPPER AND LOWER EXTREMITIES

by

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The normal anatomy of the lymphatic system was studied towards the end of the 19th and the beginning of the 20th century by injecting dye or dye-gelatin into cadavers. Some investigators employed mercury and examined the lymphatics roentgenologically. The lymph capillaries of the skin empty into increasingly larger collecting vessels which eventually form subcutaneous lymph trunks. These trunks are between 0.25 and 1 mm in diameter; they increase centrally in number by dichotomic division and finally empty into lymph nodes. No anastomoses in the ordinary sense of the term are seen between adjacent vessels. In the legs the lymph trunks accompany the great saphenous vein and the small saphenous vein.

The first roentgenograms of lymph vessels of human subjects were published some twenty-five years ago, but it was not until recently that a clinical method (KINMONTH 1954) became available for examination of the most readily accessible parts of the lymphatic system, *i. e.* the lymph vessels of the limbs, and to a certain extent the inguinal and

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Fig. 1. Axilla. Extravasations of contrast medium lie in vessels central to the first axillary lymph nodes.

axillary lymph nodes. A filling of the lymphatics of the arm is obtained following the injection of contrast medium into a vessel in the carpal or the cubital region. Filling is most readily secured of the saphena magna system by injection of contrast medium into a lymph vessel on the dorsal aspect of the foot and of the saphena parva system by injection into a lymph vessel on the lateral aspect of the Achilles region.

This paper is concerned with the normal roentgen anatomy of the lymph nodes and lymph vessels of the limbs.

Material and results

The material consisted of 80 volunteers of both sexes ranging in age from 19 to 75 years and recruited from the surgical wards, where they had been admitted mainly because of peptic ulcer or hand injuries. None of them had any known disease of the limbs examined.

Lymphograms were taken of the arms of 20 and the legs of 60 subjects. All the examinations of the arms and the first 15 of the legs were performed on one side only; in the remaining 45 subjects both legs were examined at a single sitting.

Arms. Roentgen examination of the lymphatics of the upper limbs was found to be difficult because of their small size. A filling of the lymphatics of the arm could be obtained on injection in the carpal region, but it was difficult to introduce sufficient

Fig. 2. Radial group of vessels in arm.

contrast medium to obtain roentgenograms of good quality of the axillary region. Satisfactory roentgenograms of the axillary lymph nodes were, however, obtained on injection of contrast medium in the region of the elbow (Fig. 1). As a rule, two groups of lymph vessels, a radial and an ulnar group, could be distinguished in the upper limb. The radial group (Fig. 2) extended from the dorsal aspect of the lower arm to the inner aspect of the upper arm and up to the axillary lymph nodes. The ulnar group ran in a gentle curve to the inner aspect of the upper arm and then to the axilla. We never obtained a filling of the lymph nodes in the region of the elbow.

Leys. We found the inguinal and iliac lymph nodes to show up best in films obtained immediately after the rapid injection of a relatively large amount of contrast medium. Part of the medium leaves the lymph nodes very quickly so that unless the films are taken within 1 minute of the injection, definition will be poor. On the other hand, acceptable, if not of high quality roentgenograms of the lymph vessels may still be obtained during the following ten minutes.

We usually examined the saphena magna group of vessels draining the major part of the lower leg. When the purpose of the examination was mainly to demonstrate the vessels and glands in and above the inguinal region, the contrast medium could also be injected into the vessels belonging to the vena saphena parva group. The two vessel systems emptied into different inguinal lymph nodes.

In the lower leg the lymph vessels of the saphena magna region consisted of a medial group and a lateral group. When the contrast medium was injected into a vessel situated near the medial side of the dorsal aspect of the foot, filling was, as a rule, obtained only of the medial group (Fig. 3). It was made up of but few vessels, which ran almost straight towards the medial aspect of the knee. Sometimes filling was obtained of only one vessel in the lower leg, but of an ordinary number of vessels above the knee.

When the contrast medium was injected into a vessel more laterally, filling was often obtained only of the lateral group (Fig. 4). Frequently however, both groups were outlined (Fig. 5). This was less often so

Fig. 3. Leg. Medial group.

when the contrast medium was injected into a vessel near the midline.

The lateral group of lymphatics belonging to the saphena magna system were seen to run, as they divided dichotomically, from the dorsal aspect of the foot, over the anterior aspect of the lower leg to the lateral side, whence they proceeded to the medial aspect ot the knee. In this group the vessels were more numerous and divided more frequently. No anastomoses were observed. In the frontal projection the vessels appeared to be more sparse than in the medial group. The localization and course of the medial vessels as observed in frontal projections varied insignificantly from case to case while appreciable differences were seen in the course of the vessels in the lateral group. Such variants were not considered pathologic.

From the medial aspect of the knee the lateral and the medial group of vessels accompanied the vena saphena magna with increasingly fre-

Fig. 4. Leg. Lateral group.

quent dichotomic division, so that the number of medial vessels alone were as many as 10 to 16 in the inguinal region. Both groups emptied into caudal inguinal lymph nodes.

The lymph trunks in the vena saphena parva system (Fig. 6), usually one to three in number, were seen to run along the back of the lower leg and empty into one to three lymph nodes in the popliteal fossa, whence the efferent vessels swung medially and anteriorly and ran along the medial part of the thigh together with the saphena magna group of vessels to empty into lymph nodes situated deeper than, and more cranial to those belonging to the saphena magna group. The two systems did not appear to be in communication with one another during their courses in the leg and we never observed any passage of contrast medium between the two systems. They emptied into different groups of lymph nodes in the groin. Whether the vessels and nodes central to the groin are common to both groups has not been cleared up roentgenologically but they are so described in textbooks on anatomy (BARTELS 1909, JOSSIFOW 1930). The inguinal lymph nodes showed up well in the roent-

Fig. 5. Leg. Medial and lateral group. Inguinal lymph nodes.

genograms. A filling was also often obtained of efferent vessels and more centrally located lymph nodes. The density was, however, often too high in the caudal lymph nodes and too low in the cranial lymph nodes to permit differentiation of detail within them.

Discussion

The diameter of the subcutaneous lymph trunks varies between 0.25 and 1 mm. Despite branching, the width of the vessels does not change appreciably. The valves often appeared as distinct rounded swellings about 0.5 to 1 cm apart; injected air bubbles were readily distinguished. In the present material the collecting vessels showed no change in calibre, abrupt interruption, marked tortuosity, retrograde filling, nor centripetal arborization. Neither was any filling obtained simply of a single vessel from the site of injection to the groin or axilla. Accumulations of contrast medium, sometimes present outside the normal lymph vessels, are difficult to interpret. Such accumulations are occasionally observed after trauma, *e. g.* contusions affecting the lymphatics. It is possible

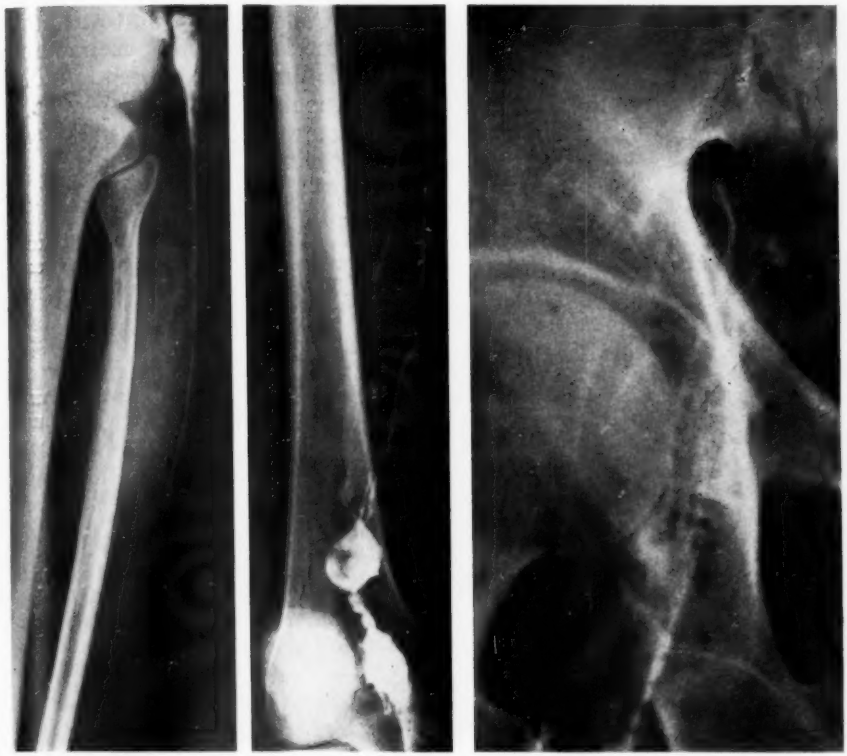

Fig. 6. Leg. Vena saphena parva group (oblique position of leg). Popliteal lymph nodes.

that they may not always be pathologic. A certain escape of contrast medium must be expected if the examination is prolonged. This appears in the roentgenogram as a diffuse veil along the entire vessel or in the early stages of the examination along a short segment. McMaster (1932), who injected dyes into the lymphatics of rats, pointed out that occasionally small extravasates occur around the lymphatics, and then usually before the passage of the dye through the wall of the entire vessel. He was unable to offer any explanation for this phenomenon, which he did not, however, consider pathologic. The difficulty is to decide as to what may be regarded as a physiologic variant and what should be considered an extravasation caused by changes in the lymph vessels. Kaindl et coll. (1957) regard local extravasation of contrast medium as pathologic.

In some cases it is possible, as shown by COLLETTE (1958), to demonstrate changes in the lymph nodes but further elaboration of the method is required for its establishment as a reliable diagnostic procedure. The most important requirement for the refinement of lymphography as a diagnostic tool is the availability of better contrast media.

SUMMARY

Experiences gained in 20 roentgen examinations of the lymphatics of the arms and in 60 examinations of the lymphatics of the legs of normal subjects, are presented and discussed. The roentgen anatomy of the lymph vessels in the limbs is described.

ZUSAMMENFASSUNG

Erfahrungen, die bei 20 Röntgenuntersuchungen der Lymphwege der Arme und bei 60 Untersuchungen der Lymphbahnen der Beine bei normalen Individuen gewonnen wurden, werden vorgelegt und diskutiert. Die Röntgenanatomie der Lymphgefässe in den Gliedmassen wird beschrieben.

RÉSUMÉ

Les auteurs présentent et étudient les résultats qu'ils ont obtenus dans 20 examens radiographiques des lymphatiques du membre supérieur et dans 60 examens des lymphatiques du membre inférieur de sujets normaux. Ils décrivent l'anatomie radiologique des vaisseaux des membres.

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PATENT PRIMITIVE TRIGEMINAL ARTERY STUDIED BY CEREBRAL ANGIOGRAPHY

by

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The most common anomalous anastomosis between the areas supplied by the carotid and vertebral arteries is a vessel, usually of large size, at the site of the cavernous sinus. This vascular communication, which in the opinion of many investigators is identical with the primitive trigeminal artery, has been known to anatomists for more than a century. About twenty anastomoses of this kind have been demonstrated by carotid angiography since 1950. Most of these cases have been described by KRAYENBÜHL & YAŞARGIL, who have also made a complete review of the anatomical and roentgenologic literature. Certain features not previously treated seem to justify the presentation of a report on our eight cases. Two of these cases have already been briefly described by LINDGREN and HÖÖK.

Case reports

Case 1. A woman, aged 41, who had suffered from migraine since childhood was submitted to roentgen examination because of right-sided hemiparesis and various neurologic signs on the left side, which included astereognosis and adiadochokinesia. Lumbar puncture revealed a subarachnoid haemorrhage.

Angiography of the left internal carotid artery showed a wide communication between the carotid and basilar arteries at the level of the cavernous sinus. The posterior

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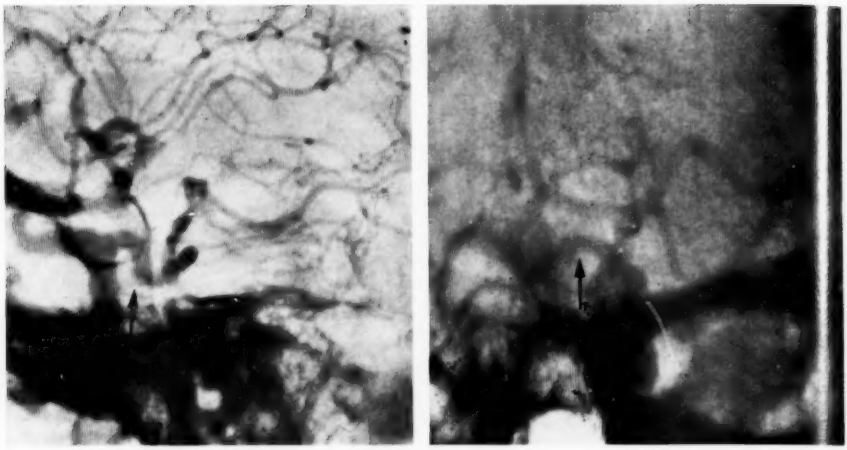

Fig. 1. Case 1. Carotid angiography. Filling of a wide primitive trigeminal artery (→). Contrast medium passed through this communication and filled the basilar artery and the superior cerebellar and posterior cerebral arteries on both sides. Lateral and a. p. views.

cerebral and superior cerebellar arteries were contrast-filled through this anastomosis. A very narrow posterior communicating artery was possibly also filled, but in comparison with the abnormal anastomosis this vessel obviously played little part in supplying the area covered by the vertebral artery. Carotid angiography on the opposite side showed no signs of abnormality. Angiography of the vertebral artery was not performed.

Case 2. A man, aged 60. One week after a moderately severe head injury, headache developed and a week later nausea and stiffness of the neck. He had no other neurologic symptoms. Lumbar puncture revealed a subarachnoid haemorrhage.

Angiography of the left internal carotid artery showed a wide anastomosis between the internal carotid and basilar arteries, approximately at the site of the cavernous sinus. The basilar artery was filled distal to the anastomosis as well as the superior cerebellar and posterior cerebral arteries on both sides. The presence of a posterior communicating artery could not be definitely established. Carotid angiography on the opposite side revealed nothing abnormal. Angiography of the vertebral artery was not carried out.

Case 3. A woman, aged 50, was examined because of a subarachnoid haemorrhage that had occurred one year previously.

Angiography of the left common carotid artery demonstrated that there was an anastomosis nearly as wide as the internal carotid artery between the latter vessel and the basilar artery, at the level of the cavernous sinus. The basilar artery as well as the superior cerebellar and posterior cerebral arteries on both sides were filled with contrast fluid. There was no filling of the posterior communicating artery. Nothing of interest was obtained from angiography of the common carotid artery on the other side. Angiography of the vertebral artery was not performed.

Case 4. A man, aged 41, had had repeated fainting attacks for over a year. Lumbar puncture yielded nothing of interest. The clinical diagnosis was epilepsia tarda.

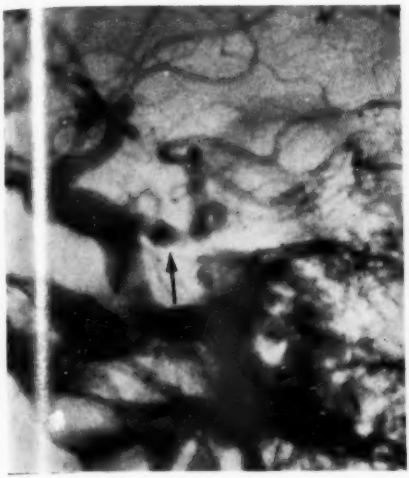

Fig. 2. Case 2. Carotid angiography. Filling of a wide primitive trigeminal artery (→). The basilar artery and the superior cerebellar and posterior cerebral arteries on both sides were filled through this anastomosis.

Fig. 3. Case 3. Carotid angiography. Filling of a very wide primitive trigeminal artery (→). A relatively narrow basilar artery and the superior cerebellar and posterior cerebral arteries on both sides were filled through this communicating vessel.

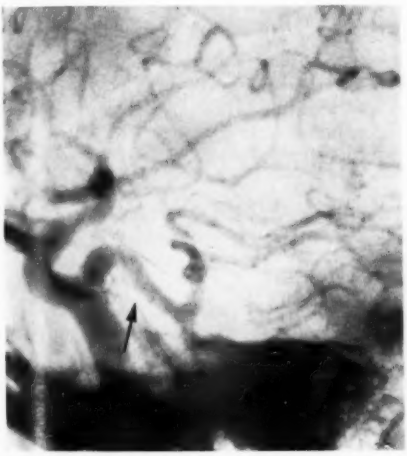

Fig. 4. Case 4. Carotid angiography. Filling of a wide primitive trigeminal artery (→). Through this anastomosis, contrast medium passed to the basilar artery and the superior cerebellar and posterior cerebral arteries on both sides. Lateral and a. p. views.

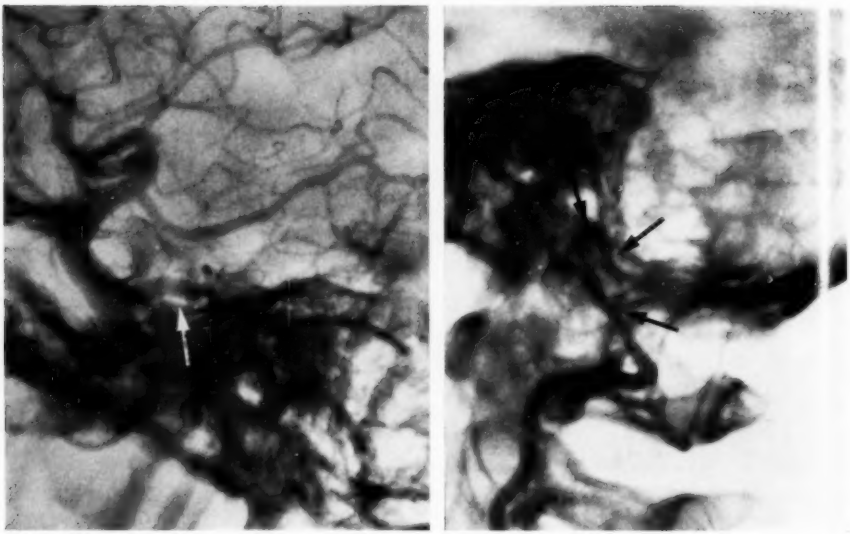

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Fig. 5. Case 6. a) Carotid angiography. Filling of a wide primitive trigeminal artery (→). Only a short section of the basilar artery, with the superior cerebellar artery on both sides, were filled through this vessel. Filling of the posterior cerebral artery took place through a fairly wide posterior communicating artery of the same width as the posterior cerebral artery. The latter vessel thus looked as if it were a branch of the carotid artery. b) Angiography of the vertebral artery showed that this vessel was relatively narrow. Only the inferior posterior cerebellar artery was filled through it.

Angiography of the right internal carotid artery revealed a wide anastomosis between the internal carotid and basilar arteries at the level of the cavernous sinus. Contrast medium passed into the posterior cerebral and superior cerebellar arteries on both sides through this communication. The posterior communicating artery was not filled. Carotid angiography on the left side showed no pathologic features. Angiography of the vertebral artery was not carried out.

Case 5. A woman, aged 69, was admitted suffering from acute symptoms of high intracranial pressure. The results from a lumbar puncture were negative. A malignant glioma in the left frontal lobe was diagnosed.

Angiography of the left common carotid artery demonstrated that there was a highly vascularized expansive process slightly larger than a walnut and with numerous arteriovenous fistulas in the left frontal lobe. In addition there was a wide anastomosis between the internal carotid and basilar arteries at the site of the cavernous sinus. Contrast medium passed through this anastomosis into the posterior cerebral and superior cerebellar arteries on both sides. No filling of the posterior communicating artery was seen. No other angiographic examinations were made.

Case 6. A man, aged 23, was examined because of visual disturbance and nystagmus. No pathologic findings were obtained from a lumbar puncture. The clinical diagnosis was atypical encephalopathy.

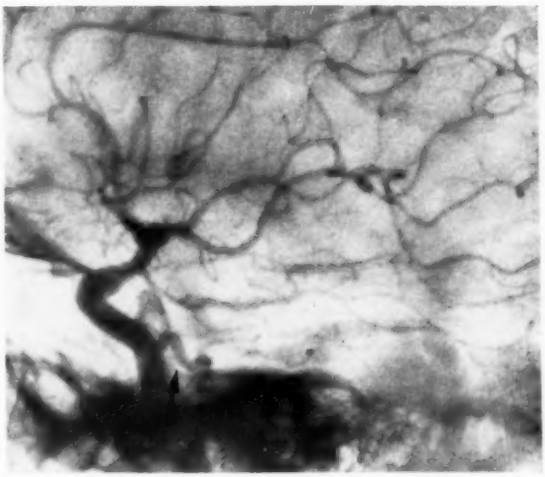

Fig. 6. Case 7. Carotid angiography. Filling of a primitive trigeminal artery (→), which was slightly narrower than in the other cases. The superior cerebellar artery on both sides was filled through this vessel. The posterior cerebral artery was filled through a posterior communicating artery of ordinary width. These two vessel-sections were of approximately the same width.

Angiography of the left internal carotid artery gave evidence of a fairly wide anastomosis between the internal carotid artery and the area supplied by the vertebral artery at the same site as in the other cases. This vessel supplied the superior cerebellar artery on both sides. A fairly wide posterior communicating artery was also shown. Contrast medium had flowed through the latter vessel to the posterior cerebral artery. Angiography of the left vertebral artery showed that this vessel supplied only the inferior posterior cerebellar artery, but not parts of the vertebral artery area situated further toward the distal aspect. Carotid angiography on the right side gave negative results.

Case 7. A man, aged 32, had had a subarachnoid haemorrhage one month before the roentgen examinations.

Angiography of the left internal carotid artery showed a fairly wide vascular anastomosis between the internal carotid and the vertebral artery area at the same site as in the other cases. A short segment of the basilar artery as well as the superior cerebellar artery on both sides, were filled by way of this communicating vessel. The posterior cerebral artery was filled, for the most part at least, through the posterior communicating artery. Angiography of the vertebral artery was not carried out. An angiographic examination of the internal carotid artery on the opposite side showed no signs of abnormality.

Case 8. A man, aged 55, was examined because of symptoms suggesting raised intracranial pressure. Lumbar puncture yielded nothing unusual. The diagnosis was right-sided frontal meningioma with a parasagittal site.

Angiography of the right common carotid revealed an anastomosis between the internal carotid and basilar arteries at the site of the cavernous sinus. Contrast medium passed

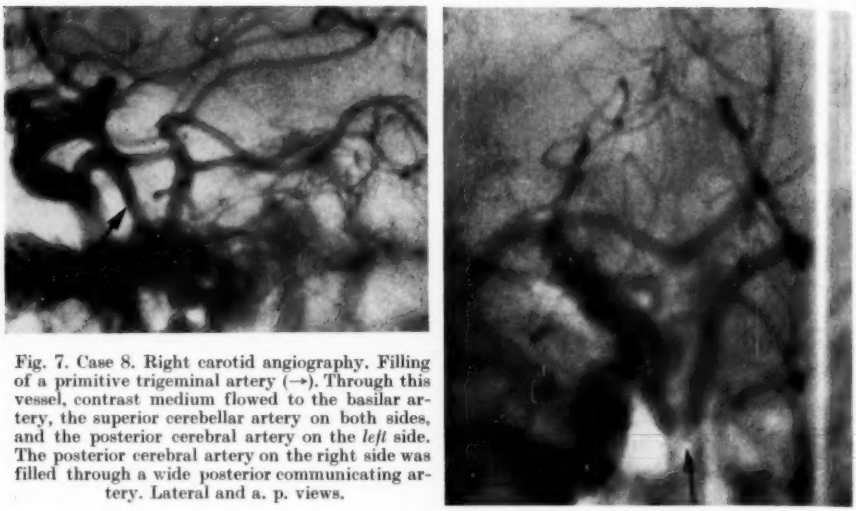

Fig. 7. Case 8. Right carotid angiography. Filling of a primitive trigeminal artery (→). Through this vessel, contrast medium flowed to the basilar artery, the superior cerebellar artery on both sides, and the posterior cerebral artery on the *left* side. The posterior cerebral artery on the right side was filled through a wide posterior communicating artery. Lateral and a. p. views.

through this communication to the posterior cerebral artery on the *left* side and the superior cerebellar artery on both sides. The posterior cerebral artery on the right side was filled through a wide posterior communicating artery. Carotid angiography on the other side showed no abnormal features. Angiography of the vertebral artery was not performed.

These eight cases had several features in common, namely that the carotid-basilar anastomosis was of the primitive trigeminal artery type, the superior cerebellar arteries on both sides received their blood supply, or at least the greater part of it, through the anastomosis; furthermore, a vertebral artery was present and had as its main task the supplying of the inferior posterior cerebellar artery. The last-named feature was verified in one case (Case 5). In the other cases, filling of the inferior posterior cerebellar artery was not seen in connection with carotid angiography and thus this vessel probably received its blood through the vertebral artery.

Two different types of this malformation could be distinguished, however. The one type (Cases 1, 2, 3, 4 and 5) was characterized by the fact that the entire vertebral artery system distal to the anastomosis was supplied through this communication. In these cases, there was poor filling of the posterior communicating artery. As regards the other type (Cases 6 and 7), the anastomosis mainly supplied the superior cerebellar artery on both sides while the posterior cerebral artery received its blood through the posterior communicating artery. Filling of the uppermost part of the basilar artery was not established with certainty in these

cases. Case 8 was a combination of the two types. In this patient the posterior cerebral artery received its blood through the posterior communicating artery, while the anastomosis supplied the superior cerebellar artery on both sides and the posterior cerebral artery on the opposite side.

The clinical significance of these anastomoses has been discussed by a few investigators. HARRISON & LUTRELL, KLOOS and HÖÖK have each described one case with subarachnoid haemorrhage. Supporting their views on the histologic observations of other authors, they consider it possible that these persisting embryonic blood vessels may have structural defects in their walls likely to involve a predisposition to aneurysm or ruptures.

In one half of our cases (Cases 1, 2, 3 and 7) the roentgen examination was carried out because the patient had had a subarachnoid haemorrhage. No aneurysm was established in connection with bilateral carotid angiography. Although angiography of the vertebral artery was not carried out in these cases, they nevertheless gave support to the view that a patent primitive trigeminal artery can give rise to subarachnoid haemorrhages.

The other four cases, however, were examined for other reasons, and the patent primitive trigeminal artery was then discovered incidentally, and probably had no connection with the patients' symptoms. There is therefore no justification for breaking off the examination of a patient with subarachnoid haemorrhage merely because an anastomosis of this kind has been observed. The possibility that there may be some other reason for the haemorrhage should always be borne in mind and the entire intracranial space carefully explored by angiography.

The necessity for a thorough angiographic investigation is even greater if surgical closure of these anastomoses or ligation of a carotid artery is to be undertaken. As there are at least two different anatomic variants, as well as combinations of the two forms, the anatomical conditions should be known in advance in order to avoid endangering the blood supply to any area.

SUMMARY

Eight cases with a patent primitive trigeminal artery are described. Two different groups of this defect can be distinguished. The clinical significance of the anomaly is discussed and stress is laid on the importance of a thorough angiographic exploration.

ZUSAMMENFASSUNG

Acht Fälle mit einer offenen primitiven Arteria trigem. werden beschrieben. Zwei verschiedene Gruppen dieses Defektes können unterschieden werden. Die klinische Bedeutung der Anomalie wird diskutiert, wobei besonders auf die Wichtigkeit einer vollständigen angiographischen Untersuchung hingewiesen wird.

RÉSUMÉ

Description de huit cas d'artère trigéminale primitive perméable. On peut distinguer deux groupes différents de cette malformation. L'auteur examine l'intérêt clinique de cette anomalie et insiste sur l'importance d'un examen angiographique complet.

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FROM THE SURGICAL AND RADIOLOGICAL SERVICES, VETERANS ADMINISTRATION HOSPITAL, BRONX 68, N. Y., U. S. A.

COSTAL INTRA-OSSEOUS ANGIOCARDIOGRAPHY

by

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and *Philip Cooper*

It is the purpose of this communication to present a new method for the contrast examination of the cardiac chambers and great vessels. The approach under consideration is technically simple and requires no elaborate instrumentation. It also has the advantage of yielding valuable information on the roentgen anatomy and hemodynamics of certain venous pathways not encompassed by the conventional intravenous angiocardiography. Furthermore, it represents a readily available route when, for some reason, selective angiocardiography or the usual intravenous method is not feasible. The present report will deal exclusively with the normal heart.

Technique

The usual precautionary tests against possible idiosyncrasy to the contrast substance must be carried out. The medium employed in this study was a 50 % solution of Hypaque (sodium 3,5 diacetamido-2, 4, 6 triiodobenzoate) (generously made available through Winthrop Lab. Inc., N. Y.) which has been found to be remarkably free of untoward side effects and

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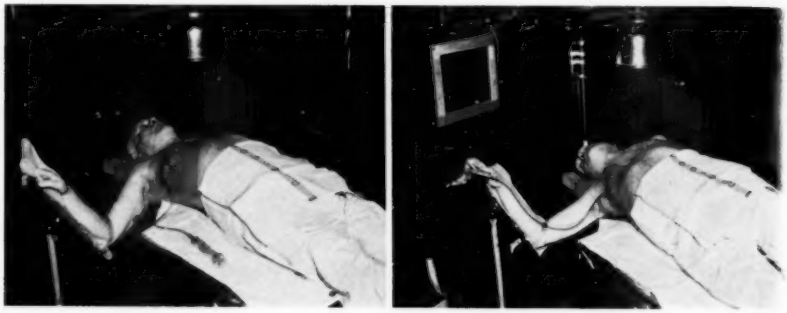

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Fig. 1. a) Positioning of patient in the antero-posterior projection. b) Right posterior oblique position. Patient rotated 45 degrees. The length of plastic tubing allows adequate shielding of the examiner.

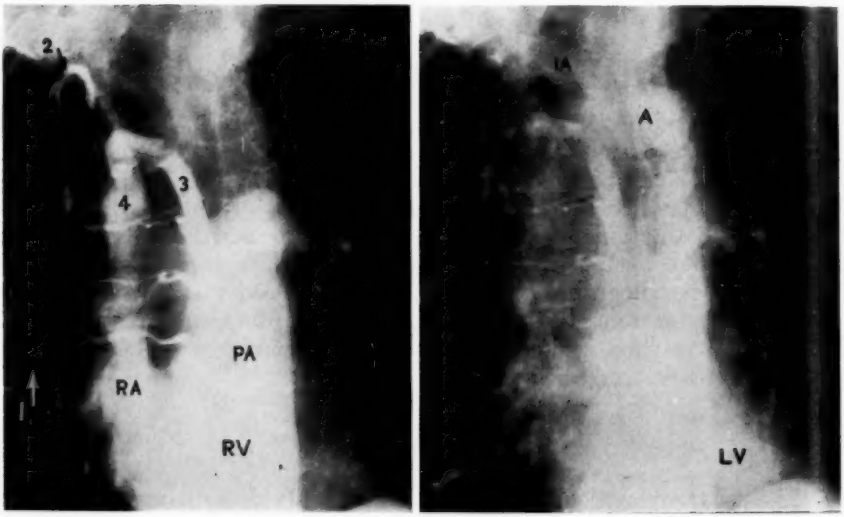

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Fig. 2. Injection into seventh rib. a) Antero-posterior view of heart and great vessels at three seconds. First film exposed after the injection of 20 ml of a total dose of 50 ml Hypaque. b) Angiocardiogram at twelve seconds. Residual filling of intercostal veins and azygos veins even after the end of injection accounts for the faint visibility of the pulmonary artery at this stage. 1 — intercostal veins, 2 — right internal mammary vein, 3 — azygos vein, 4 — superior vena cava, RA — right atrium, RV — right ventricle, PA — main pulmonary artery, IA — innominate artery, A — aorta, LV — left ventricle.

Fig. 3. Injection of contrast medium into fifth rib. Antero-posterior projection at three seconds. First exposure taken after injection of 20 ml of Hypaque. 1 — right subclavian vein, 2 — right innominate vein, 3 — intercostal veins, 4 — right internal mammary vein, 5 — arch of azygos vein, 6 — paravertebral veins.

to yield a very satisfactory contrast. The patient is sedated with meperidine hydrochloride (100 mg) and secobarbital sodium (100 mg) one hour prior to the procedure, which is performed on an empty stomach.

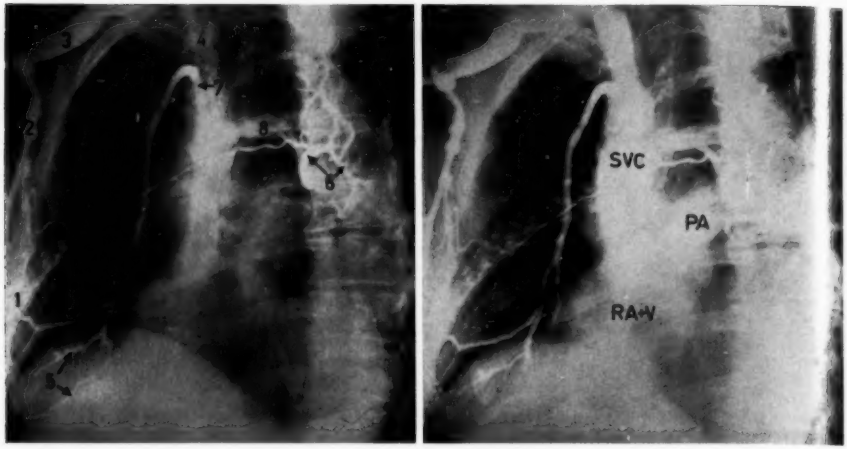
The supine patient is properly positioned, on an automatic rapid cassette changing device, with the right arm elevated and adequately supported (Fig. 1 a). After preparation of the right lateral chest wall, the proposed site of injection is anesthetised with 2 % Procaine down to and including the periosteum of the selected rib.

We have found the fourth to seventh rib in the right anterior axillary line to be the best sites for injection.

A 16 gauge Rosenthal bone marrow needle (BD 460 LNR, or its longer version BD 461 LNRC for obese patients) is introduced, with a rotary motion, into the medullary cavity of the rib. The aspiration of bone marrow which, like the injection, is always accompanied by a sensation of local 'pressure' confirms the correct positioning of the needle. Two to three milliliters of 2 % Procaine are then injected directly into the medullary cavity. This technique is similar to the one previously described for intra-osseous venography (See References) except that a 2 % solution of Procaine is now employed, rendering the procedure practically painless.

At the level of the fourth to sixth rib, the pectoral fascia appears as a thick band called the suspensory ligament of the axilla. This fascia may be so firm as to be mistaken for the rib. By further advancing the needle solid bone is encountered. The properly placed needle is firmly fixed by the pectoral fascia and outer cortex of the rib. Nevertheless, any brisk or wide range motion of the right arm should be avoided since the needle may be displaced by the sheering action of the pectoral muscles and fascia.

The needle is connected to a 50 ml manual syringe by a piece of flexible plastic tubing, and 50 ml of contrast medium injected as rapidly



a b

Fig. 4. Same patient as in fig. 3. Right posterior oblique position. a) Angiocardiogram at one second. Contrast substance just reaching right atrium. b) Angiocardiogram at three seconds. Right side of heart and pulmonary artery outlined. 1 — medullary cavity of fifth rib, 2 — right lateral thoracic vein, 3 — right axillary vein, 4 — right innominate vein, 5 — intercostal veins, 6 — paravertebral veins, 7 — right internal mammary vein, 8 — arch of azygos vein. SVC — superior vena cava, RA & V — right atrium and right ventricle, PA — pulmonary artery.

as possible. The duration of injection may vary with the degree of osteoporosis or osteosclerosis of the rib but averages eight seconds. A series of 12 roentgenograms taken at an interval of one second, and with the first film exposed after 20 ml of contrast medium have been injected, has been found to yield the desired information.

An identical injection is repeated after the patient has been rotated 45 degrees into the right posterior oblique position and adequately supported by foam rubber cushions (Fig. 1 b). Although not necessary, it is advisable to disconnect the plastic tubing from the needle during the repositioning of the patient. After completion of the injection the needle is withdrawn. No special aftercare is required.

Discussion

The introduction of contrast medium into the medullary cavity of the fourth to seventh rib in the right anterior axillary line outlines the cardiac chambers and great vessels to a satisfactory degree (Figs. 2 to 4). The main difference between the two levels of injection is that the filling of the heart occurs principally through the azygos and internal mammary

veins, and less through the subclavian vein if a lower rib is chosen (Fig. 2a). If the fourth rib is injected the filling of the cardiac chambers occurs somewhat less through the azygos vein and more via the internal mammary and subclavian veins (Figs. 3 and 4). The difference is probably due to the fact that the azygos vein ends as it arches over the right main stem bronchus more or less at the level of the fifth dorsal vertebra. As demonstrated in Figs. 3 and 4a only the arch of the azygos vein is visible after the injected contrast medium has reached it through the intercostal veins and vertebral plexus.

Additional vascular pathways, well outlined by the injection of contrast medium into the fifth rib, are the lateral thoracic vein which joins the axillary vein, the intercostal veins leading anteriorly into the ipsilateral internal mammary vein, and posteriorly into the uppermost portion of the azygos vein through the paravertebral veins. If the seventh rib is injected, more of the ascending portion of the azygos vein is contrast-filled, with little or no filling of the vertebral plexus (Fig. 2a). The well established fact that the human venous system is subject to a number of anatomical variations is also illustrated by the different appearances of the internal mammary veins in two different patients (Figs. 2a and 4a).

The present study again demonstrates that the intramedullary introduction of a substance corresponds, for all practical purposes, to an intravenous injection. Furthermore, it illustrates the potentialities of intra-osseous venography not only as a valuable diagnostic means, but also as an approach to the investigation of anatomical and physiological characteristics of certain venous pathways which escape evaluation by other conventional methods.

SUMMARY

The authors present and discuss a new method of angiocardiography which consists of the injection of contrast medium into the fourth to seventh rib in the right anterior axillary line. The proposed approach also permits the simultaneous roentgenographic demonstration of additional extra- and intrathoracic venous channels such as the lateral thoracic, axillary, subclavian, intercostal, internal mammary and azygos veins as well as portions of the dorsal vertebral venous plexus.

ZUSAMMENFASSUNG

Die Verfasser präsentieren und diskutieren eine neue Angiokardiographiemethode, welche in der Injektion des Kontrastmittels in die 4. bis 7. Rippe in der rechten vorderen Axillarlinie besteht. Die vorgeschlagene Injektionstechnik gestattet auch den gleichzeitigen röntgenologischen Nachweis anderer extra- und intrathorakaler Venen wie die V. thoracalis lateralis, V. axillaris, V. subclavia, Venae intercostales, V. mammaria interna und die V. azygos sowie von Abschnitten des dorsalen venösen Plexus vertebralis.

RÉSUMÉ

Les auteurs présentent et étudient une nouvelle méthode d'angiocardiographie qui consiste à injecter le moyen de contraste dans la quatrième — la septième côte, sur la ligne axillaire droite. La voie d'injection proposée permet aussi de mettre en évidence radiographiquement, en même temps, d'autres trajets veineux extra- et intrathoraciques, tels que les veines thoraciques latérales, axillaire, sous-clavière, intercostales, mammaire interne et azygos, ainsi que des parties du plexus veineux vertébral dorsal.

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FROM THE ROENTGEN CLINIC (DIRECTOR: PROF. Z. KUBRAKIEWICZ) AND THE INSTITUTE OF ANATOMY (DIRECTOR: PROF. T. MARCINIAK) OF THE MEDICAL ACADEMY, WROCLAW, POLAND

METOPISM AND ITS CORRELATION WITH THE DEVELOPMENT OF THE FRONTAL SINUSES

A roentgen-anatomic study

by

Roman Marciniak and *Czeslaw Nizankowski*

The metopic suture is often encountered in roentgenograms of the adult skull. It is to be seen partially or completely in the postero-anterior view of the skull and in the projections for the accessory nasal sinuses as a linear translucency, sometimes with indentations, running through the middle part of the frontal bone from the root of the nose to the bregma. The suture is a normal developmental stage in children and when persisting in adults has been dealt with by several anatomists and anthropologists. From the roentgenologic point of view the metopic suture constitutes a normal developmental variety without any clinical importance.

What is of interest both to the roentgenologist and the anatomist is the relationship between the metopic suture and the development and differentiation of the frontal sinuses; this relationship, which is referred to as 'metopism' is a controversial problem. SAMUEL (1952), WELIN (1952), HODGSON (1957) among others, claim that the presence of the metopic suture is mostly associated with the congenital absence or underdevelopment of the frontal sinuses. MURCZYŃSKI (1957) in his recent paper on the morphogenesis of the frontal sinuses postulates that the

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relationship between the metopic suture and congenital absence of the frontal sinuses is a doubtless fact, included in all textbooks. This point of view, which has been accepted by roentgenologists of the old anatomical school, is not confirmed by the studies of HAAS (1933), ROCHLIN and RUBASCHEWA (1934), MONTEIRO and RAMOS (1954), and TORGERSEN (1950).

The present paper is concerned with the analysis of this relationship based upon data on the development of the frontal bone and frontal sinuses as well as on our own observations made on living and museum material. The analysis requires a short survey of the anatomy of the development of the frontal bone and frontal sinuses.

The frontal bone as a membrane bone is developed within the desmocranium towards the end of the second month of foetal life from two separate nuclei situated in the region of the future frontal tubera. Both halves of the frontal bone are separated by the suture which at the end of the first month of postnatal life is obliterated from its middle part to the root of the nose and bregma. The suture is not evident clinically in a 2-year-old child. The total fusion of both parts of the frontal bone takes place towards the end of the 10th year of life. In some cases the suture at first pursues a winding course and then becomes typically serrated without any tendency to obliteration. The indentation pattern is very marked within the outer table. The formed and preserved suture running from the root of the nose to the bregma is referred to as a persistent frontal suture (MARTIN) or metopic suture.

As compared with other sutures, the disappearance of which begins with the sagittal suture as early as at about 30 years of age, the metopic suture exhibits the least tendency to disappear in advanced age.

Skulls exhibiting the metopic suture are termed by anthropologists crania metopica (MARTIN) or crania bifida (TERRAFRANCA). A so-called metopic fontanelle which may contain the metopic bone may occasionally be observed in the lower portion of the metopic suture at the level of the root of the nose, or more rarely in its middle part below the line connecting the two frontal tubera.

The metopic suture is to be differentiated from the so-called metopic fissure, the latter being the remainder of the anterior branch of the anterior fontanelle. The persistent metopic suture shows a rapid obliteration only in man, monkey, elephant, and bat; in other mammals it remains open. According to TORGERSEN (1951) it is inherited as a dominant trait. A metopic suture is often accompanied by the additional bones termed interparietal bones. They manifest the same genetic features.

The percentage incidence of the metopic suture in particular races and nationalities as well as the age and sex distribution were studied mostly in museum and diluvial material by anatomists and anthropologists.

From the literature data reviewed by MARTIN and VAN ACKEN the suture is encountered in:

Negroes and Australians	in	1.0 %	(Bartels, Anutschin)
Malayans	"	2.8 %	(Anutschin)
Slavs	"	6.4 %	(Gruber)
Russians	"	8.0 %	(Popow)
Germans	"	12.3 %	(Welcker)

The numerical divergences are due not only to the race variances but also to variations in the methods and their precision as well as to the varying interpretation of the conception of the suture.

The German investigators WELCKER and ANUTSCHIN believe that the metopic suture is more often encountered in races with a high cultural level. These authors are of the opinion that the metopic suture occurs in skulls with broad foreheads, the latter being connected with a higher development of the frontal lobes, which means with higher intellectual power.

The development of the frontal sinuses is not directly related to that of the frontal bone. The frontal sinuses like the maxillary sinuses and ethmoidal cells are formed by the invagination of the endothelium which covers the lateral wall of the nasal cavity. The developmental stage of the frontal sinuses may be divided into 2 periods: foetal and postfoetal.

In the foetal stage the endothelium of the lateral nasal wall is invaginated by about the 4th or 5th month of life at the level of the future middle meatus of the nose, a small vesicular pouch thereby being formed. This pouch is directed upwards and medially, giving origin to the ethmoidal and frontal sinuses. Towards the end of the 5th month of foetal life a more or less marked differentiation of this pouch takes place and histologic examinations will even at this stage reveal the rudiments of the particular sinuses. According to HAJEK a so-called secondary growth of the frontal sinuses also occurs; this consists in the invagination of the vesicles of the ethmoidal sinuses into the frontal bone; the frontal sinuses thus formed join the nasal cavity indirectly via the ethmoidal sinuses.

In the postfoetal period the growth of the frontal sinuses undergoes considerable individual variations (TANEW). At birth the maxillary and ethmoidal sinuses are already well differentiated whereas the frontal sinuses make their appearance mostly towards the end of the first month of life. The frontal sinuses grow slowly and reach full development only in the 20th year of life. The growth of the frontal sinuses is accompanied by the development of the nasal part of the frontal bone and contributes at puberty to the change in physiognomy by the conversion of the concave child forehead into the flat one of adults. The interpretation of the incidence of the frontal sinuses and their expression in the roentgenologic

pattern varies from author to author. ONODI stated that the frontal sinuses in a 15-month-old child reach 4 mm. RICHTER found that they were present in a 2-year-old child, and STEINER and SPEE in children between the first and second year of life. According to MONTI the sinuses make their appearance in about the 3rd to 4th year of life and to ENGEL in the 12th month of life; HARTMANN observed them at puberty. The final size of each frontal sinus, achieved in about the 20th year of life, is about 21 mm in height; according to ONODI it may reach 36 mm. The width ranges from 24 mm (MARTIN) to 25 mm (ONODI), and the depth varies from 16 mm (MARTIN) to 18 mm (ONODI). The sinuses are pyramidal in shape.

Distinct recesses of the frontal sinuses are commonly encountered. The sinus becomes invaginated in the orbital part of the frontal bone as the orbital recess and in the squamous part of that bone as the squamous recess. In addition membranous septae may originate from the bone ridges and project into the lumen. The septae may partially or wholly divide the sinus into smaller cavities, complete membranous septae being rare in man. The frontal sinuses are mostly asymmetric, being better developed on the left than on the right side (in 67 % of subjects).

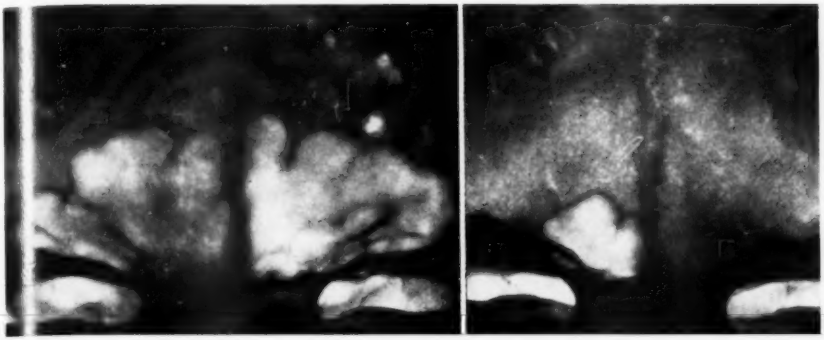
Congenital absence of the frontal sinuses is in MARTIN's opinion found in about 7 % of Europeans and 30 % of Australians. Anthropologic studies revealed no relationship between the growth of the frontal sinuses, their size, the shape of the supraciliary ridges, and the type of the skull.

The reasons accounting for the inhibition of pneumatisation in the growth of the frontal sinuses have not been adequately explained. There are a number of hypotheses of which the most plausible is the one advanced for the explanation of the arrested pneumatisation of the mastoid processes. Supporters of that theory (*e. g.* HAAS) attribute the inhibited pneumatisation to inflammatory states during primary growth, ozaena being considered as the most important causative factor. Supporters and opponents of this theory alike have not been able to establish a higher incidence of metopic suture associated with congenital absence of the frontal sinuses.

Table 1

(*After* ROCHLIN *and* RUBASCHEWA *1934*)

Skulls		Congenital bilat. absence of front. sin.		Congenital unilat. absence of front. sin.	
Type	Number	Number	%	Number	%
Metopic	110	31	28	18	16.3
Control (Various)	80	6	7.5	9	11.2
Control (Russian)	100	7	7	4	4



a b

Roentgenograms illustrating the occurrence of the metopic suture. a) Well developed frontal sinuses. b) Unilateral frontal sinus.

The roentgenographic appearances of a metopic suture are characteristic. It is rarely to be seen throughout its course; the lower supranasal part of the suture is usually absent; the same is true for the metopic fissure which, however, is seldom visible in roentgenograms. The suture is better shown in the p. a. view than in the half-axial projections. The suture in the obliteration stage, which consists in the sclerosis of bone at the suture edges and of the diploic structure, is more readily demonstrated.

The roentgenographic appearances do not confirm the anatomical classification of the obliteration type as applied by BROCKA.

The suture need not necessarily follow the middle line; it may show some deviations (BARDERLEBEN). In TORGERSEN's opinion the suture is more often deviated to the right than to the left.

The following must be differentiated roentgenologically: (1) Posttraumatic changes such as a linear fracture of the frontal bone and posttraumatic widening of the sagittal suture, and (2) the so-called middle occipital fissure which is occasionally encountered but due to the projection angles is less visible and less marked in p. a. views.

The roentgenologic diagnosis of a metopic suture may present certain difficulties:

1. If the suture is partially obliterated; the upper portion is the most persistent.

2. If in children the suture is masked by the occipital protuberances.

3. If in the ossification period the obliteration affects the suture on the outer table (HAAS).

4. In the case of an oblique course of the suture along the surfaces of the inner and outer tables, as is the case in some varieties of metopic suture (VAN SPEE).

Table 2

State of the sella turcica, external occipital protuberance and sphenoidal sinus aeration connected with metopic and control skulls (after ROCHLIN *and* RUBASCHEWA *1954)*

Skulls		Infantile index of sella turcica		Occipital spur	Degree of clinoid sinus aeration	
Type	Number	Number	%	%	Whole sinus aerated %	Sinus aerated in 1/3 frontal part %
Metopic	55	23	41.8	38.1	23	21.8
Control	125	9	7.2	67.2	26.2	2.4

Statistical data on the incidence of the metopic suture based upon roentgenologic studies differ from anatomical and anthropologic investigations, which rely on macroscopic observations. Taking into due consideration the fact that there will be no roentgenologic evidence of a metopic suture in a number of cases in which it exists it is to be assumed that statistics based on roentgen examinations will show a lower percentage than those resulting from anatomical observations. The incidence of metopic suture established roentgenologically are as follows:

VAN ACKEN (Germans) ..... 953 cases (8.0 %)
HAAS (museum material) ..... 400 cases (3.2 %)
MURCZYNSKI (Poles) ..... 1,189 cases (11.0 %)

The clinical importance of the suture, as far as can be gathered from articles which deal with this subject, is slight.

A higher incidence of the suture was observed in insane persons (MATERNA and GERHARD 1936, HESS 1945). TORGERSEN (1950) could not confirm these findings. His material consisted of 25 persons with hydrocephalus, 66 mentally deficient children, and 530 adults with mental disturbances. He could only establish the higher incidence of the suture in congenital myxoedema; an explanation of this may be found in the fact that there is a general delay in the ossification of all cranial sutures in this condition (WELCKER, FISCHER). HESS (1945) recommended the term 'metopic syndrome', the main feature of which is the persistence of the mediofrontal suture, accompanied by syndactyly, abnormalities in the relative length of the fingers, and other developmental abnormalities.

Many other theories have been advanced to explain the metopic syndrome by disturbances in internal secretion. Two main groups may be differentiated. There are views claiming that metopism occurs in constitutional types showing certain impairment of internal secretion,

Table 3

Comparative table based on own investigations

	Number	Metopic suture		Frontal sinuses						
				Number	Present				Absent	
					On both sides		On one side			
		No.	%		No.	%	No.	%	No.	%
Living individuals up to 20 years old examined roentgenologically	2018	252	12.4	252	214	84	18	7.1	20	8
Females	1240	168	13.5							
Males	778	84	10.8							
Neolithic skulls (Museum material)	352	26	7.39	26	21	75.5	2	10.5	3	14
Diluvial skulls (Museum material)	1,142	67	5.86	—	—	—	—	—	—	—

or reflected infantilism. This point of view was shared by ROCHLIN and RUBASCHEWA (1934). Other theories assume metopism to be the manifestation of pathologic changes resulting mainly from disturbances in internal secretion. PAPILLAUT (quoted by ROCHLIN and RUBASCHEWA) claimed that metopism is an expression of a disturbed ossification process caused by thyroid dysfunction. AUGIER (1913) attributed it to a disturbance in function of the pituitary gland. The theories of this second group are not confirmed clinically. The observations of ROCHLIN and RUBASCHEWA point to a correlation between the metopic suture and underdevelopment and congenital absence of the frontal sinuses, the inferior pneumatisation of the sphenoid sinus, infantile shape of the sella turcica, and underdevelopment of the external occipital protuberance. This correlation is shown in Tables 1 and 2.

Our own investigations were based on living and museum material. The living material comprises 2,018 skulls (films obtained in p. a. and half-axial projections) of patients seen in our clinic during a period of 3 years. Our observations are concerned with the incidence of the metopic suture with bilaterally developed frontal sinuses, a unilateral, frontal sinus, as well as with cases of congenital absence of the sinuses.

The material under investigation is made up of 778 males and 1,240 females, the ages of the patients being up to 20 years, *i. e.* the time when the growth of the frontal sinuses is complete. A persistent metopic suture was found in 84 cases (10.8 %) in males and 168 cases (13.5 %) in females.

Thus in a total of 2,018 cases a frontal suture persisted in 252 cases (12.48 %). Among these 252 skulls bilateral frontal sinuses occurred in 214 cases (84.9 %), a unilateral frontal sinus in 18 cases (7.1 %) and congenital bilateral absence of the frontal sinuses in 20 cases (8.0 %).

The investigation of the museum material covered the skull collecti ns of the Museum of the Institute of Human Anatomy, Wroclaw and he Anthropologic Institute of the Polish Academy of Sciences, Wrocl w. Among 352 skulls in the former Institute (neolithic skulls of the la 2 decades) a persistent metopic suture was noted in 26 cases (7.39 %). Among these 26 skulls bilateral frontal sinuses occurred in 21 c es (75.5 %), a unilateral frontal sinus in 2 cases (10.5 %) and congen al absence of the frontal sinuses in 3 skulls (14.0 %). The museum mate ial of the Anthropologic Institute contained 67 cases with a persistent fro al suture out of a total number of 1,042 cases (5.86 %) (Table 3).

Conclusions

1. Metopism, which normally occurs in a certain percentage of subje ts, should not be considered as a normal developmental variation but as an expression of a certain correlation syndrome in the evolutionary sense.

2. The material under investigation showed a higher incidence of metopic suture in neolithic than in the diluvial skulls. This fact is likely to confirm the anthropologic point of view which attributes to metopism evolutionary features with a progressive significance.

3. The suture is best demonstrated in p. a. views of the skull.

4. The clinical importance is negligible. The majority of clinical studies does not confirm the higher incidence of the metopic suture in mental disease.

5. In the material under investigation of the metopic suture both in living subjects (84.9 %) and museum material (75.5 %), the frontal sinuses were found in most cases to be well developed. Unilateral development and congenital absence were observed in a considerably lower number of cases.

6. The material investigated does not allow the conclusion that metopism is associated with underdevelopment of the frontal sinuses. The absence of the frontal sinuses was not more frequent in metopism than in skulls without this feature.

SUMMARY

The authors have performed roentgenologic investigations on the relationship of the incidence of a metopic suture and its correlation with the development of the frontal sinuses in a material of 2,018 cases. A metopic suture was found in 252 12.48 %) of these cases in 84.9 % of which the frontal sinuses were normally developed. Somewhat lower figures were obtained in a smaller museum materi l of neolithic skulls. No evidence was obtained that metopism is associated with unde - or non-development of the frontal sinuses.

ZUSAMMENFASSUNG

Die Verfasser haben an einem Material von 2,018 Fällen röntgenologische Untersuchungen über die Beziehungen des Auftretens einer metopischen Sutur und deren Korrelation zu der Entwicklung des Sinus frontalis durchgeführt. Eine metopische Sutur wurde in 252 (12.48 %) dieser Fälle gefunden. In 84.9 % der Fälle mit metopischen Suturen waren die Stirnhöhlen normal ausgebildet. Etwas niedrigere Werte erhielt man beim Studium eines kleinen Museummateriales neolytischer Schädel. Es konnte nicht bewiesen werden, dass der Metopismus mit einer partiellen oder totalen Entwicklungshemmung der Stirnhöhlen verknüpft ist.

RÉSUMÉ

Les auteurs ont fait des recherches radiologiques sur la fréquence de la suture métopique et sur sa corrélation avec le développement des sinus frontaux sur une série de 2,018 cas. Ils ont trouvé une suture métopique dans 252 de ces cas (12.48 %), dont 84.9 % avaient des sinus frontaux normalement développés. Ils ont trouvé des nombres un peu inférieurs sur une plus petite collection de crânes néolithiques d'un musée. Rien ne prouve que la suture métopique soit associée à un moindre développement ou à un défaut de développement des sinus frontaux.

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CAROTID ANGIOGRAPHY WITH TRI-IODOBENZOIC ACID DERIVATIVES

A comparative experimental study of the effects on the systemic circulation in cats

by

Percy Lindgren

Carotid angiography is generally known to produce various subjective and objective reactions. Although the physical manipulations associated with the injection may be of some significance, most of the side-effects are probably attributable to the contrast medium. That a major disparity may exist in the pharmacologic characteristics of different contrast media has been shown by a number of investigators. Quite recently BROADBRIDGE (1956) reported a comparison of sodium diatrizoate (Hypaque), sodium acetrizoate (Diaginol), and Diodone in carotid angiography with particular reference to complications and side-effects and pointed out that there were marked differences between the three contrast media.

It is known from other investigations that carotid angiography with iodine compounds is usually accompanied by hypotension and changes

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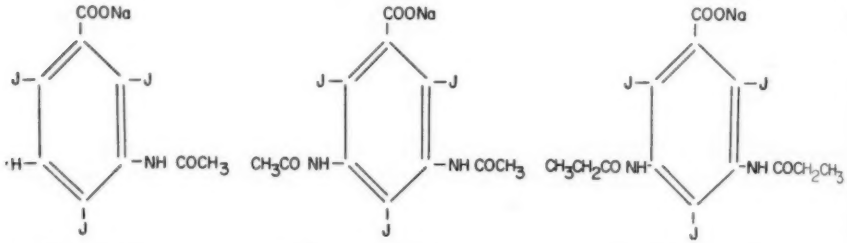
in heart rate, as was demonstrated by WEATHERALL (1942) in an experimental study in cats (Diodone and Iodoxyl). Similar falls of blood pressure have been reported by other authors including BROMAN and OLSSON (1948) with various Diodone contrast media in rabbits, BASSETT et coll. (1953) with Diodrast, Urokon, and Thorotrast in dogs and rabbits, SCHMIDT (1955) with Thorotrast, Perabrodil, Ioduron, Umbradil, and Urografin in cats and rabbits, and by GREITZ (1956) with Triurol in man. Bradycardia during carotid angiography has been observed by FOLTZ et coll. (1952) with Diodrast in man, monkeys, and cats, by GREITZ (1956) with Triurol in man, and by LINDNER et coll. (1956) with Hypaque in dogs.

Three of the latest contrast media to be introduced — sodium acetrizoate, sodium diatrizoate and sodium diprotrizoate — are derivatives of tri-iodobenzoic acid and hence are chemically similar (See below).



That they differ in pharmacologic characteristics is evident, *e. g.* from the above-mentioned paper of BROADBRIDGE. A clear difference between sodium acetrizoate and sodium diatrizoate with regard to vascular effects in peripheral arteriography was recently shown by LINDGREN and TÖRNELL (1958) (12); after the injection of 0.05 to 0.2 ml into the femoral artery in cats, sodium acetrizoate produced an increase of the blood flow in the leg several times greater than that caused by sodium diatrizoate. The present investigation was designed to compare the effects on blood pressure and heart rate of these three tri-iodobenzoic acid derivatives — sodium acetrizoate (Triurol), sodium diatrizoate (Hypaque) and sodium diprotrizoate (Miokon) in carotid angiography.

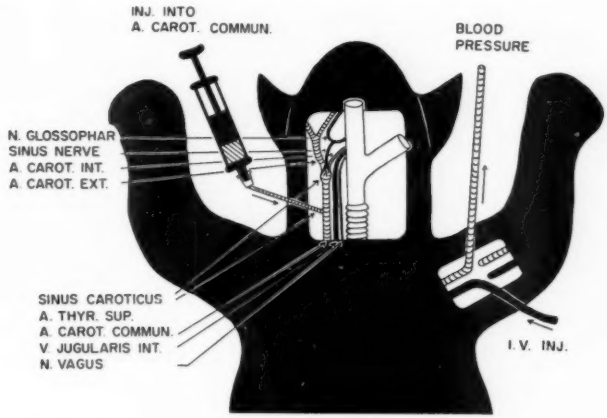


Fig. 1. Schematic representation of the preparation of the neck of the animals.

Methods

The series consists of 12 cats weighing 2.0 to 5.0 kg; average weight 3.1 kg. They were anesthetized with Dial (40 to 70 mg/kg; average 52 mg/kg).

The arterial blood pressure was recorded in the femoral artery, which was cannulated and connected with an ordinary mercury manometer. Owing to the inertia of the system the records represent the mean blood pressure; the systolic pulses caused only small although distinct fluctuations of the mercury level. At fast rates of the kymograph, the method therefore also allowed recording of the heart frequency. In order to prevent clotting in the cannula, heparine, 25 mg per kg in a 5 per cent solution, was given intravenously. After anesthetization, the trachea was dissected free and a Y-shaped tracheal cannula inserted. The common carotid artery and the vagus nerve were dissected free on either side of the trachea and a segment of each, about 2 to 3 cm long, was exposed.

The roentgen contrast media were introduced into the common carotid via a fine polyethylene tube inserted into the proximal end of the cut superior thyroid artery, or a muscular branch at the same level. The carotid circulation was thus not impaired by this procedure; in several earlier investigations the injections were made through a tube inserted into the carotid artery itself, which latter must have been ligated.

Fig. 1 illustrates the mode of preparation.

The commercial preparations, Triurol, Hypaque, and Miokon (supplied by A.B. Leo, Hälsingborg, A.B. Erco, Stockholm, and A.B. Pharmacia, Uppsala), in 50 % concentrations in all cases, were used.

Results

To obviate motor effects (localized or generalized spasm) and respiratory depression that would conceivably have a secondary influence on the circulatory apparatus, only relatively moderate amounts of contrast

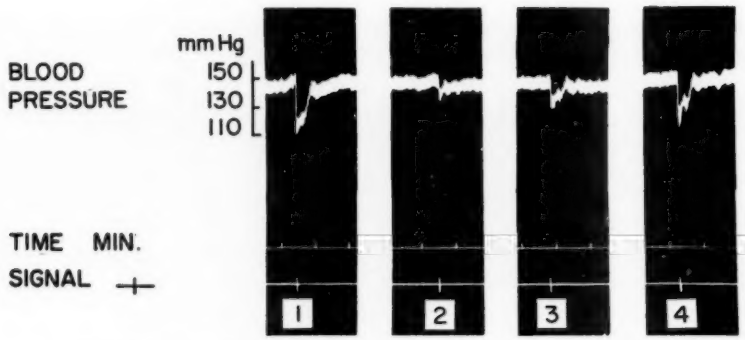


Fig. 2. Cat of 2.2 kg, Dial 55 mg/kg. Intracarotid injections of contrast media.

		Decrease in blood pressure
1. 0.2 ml sodium acetrizoate	50 % (Triurol)	35 mm Hg
2. 0.2 ml sodium diatrizoate	50 % (Hypaque)	10 mm Hg
3. 0.2 ml sodium diprotrizoate	50 % (Miokon)	15 mm Hg
4. 0.2 ml sodium acetrizoate	50 % (Triurol)	30 mm Hg

medium were injected in this series into the common carotid artery; 0.1 to 0.4 ml, *i. e.* approximately 0.05 to 0.1 ml per kg body weight.

Injection of sodium acetrizoate was usually followed, after a few seconds' latency, by a distinct fall in blood pressure and retardation of the heart rate. The quantitative differences in response between different cats were rather large. In a few cases there was no effect at all on the systemic circulation but these negative results were discarded for reasons which, together with possible causes for the wide range of values obtained, are discussed below. It should be pointed out, however, that in those experiments in which carotid angiography with sodium acetrizoate failed to influence the blood pressure and heart rate, the same was true of sodium diatrizoate or sodium diprotrizoate; exclusion of these cases does not therefore affect the comparative figures for the different contrast media.

In each of the twelve experiments in which sodium acetrizoate had a positive effect, sodium diatrizoate was injected after an interval of 10 to 15 minutes, and in the seven (chronologically last) experiments, sodium diprotrizoate as well. In most experiments two or three series of injections were given with the different contrast media. The difference in response between different injections of the same contrast medium in the same experiment was exceedingly small. There was no major correlation between dose and response in the experiments as a whole; but a far more distinct correlation in one and the same experiment.

The difference in depressor effect between the various contrast media

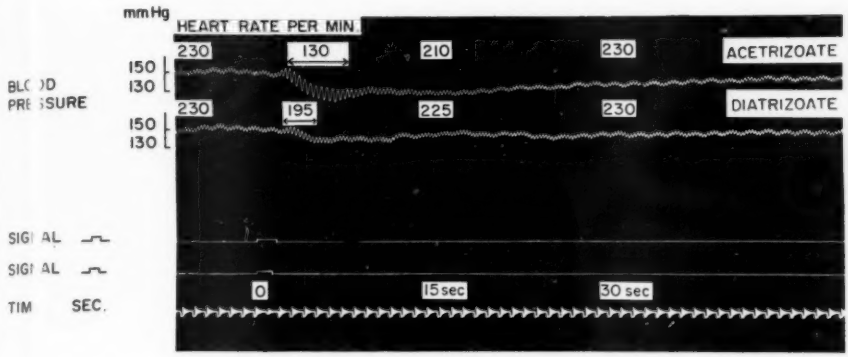


Fig. 3. Cat of 2.8 kg, Dial 45 mg/kg. Typical responses — decrease of heart rate and blood pressure — to intracarotid injection of 0.1 ml sodium acetrizoate (upper record) and 0.1 ml sodium diatrizoate (lower record). Quantitative differences between the two responses are apparent.

is illustrated in Fig. 2. In this cat, 0.2 ml sodium acetrizoate produced a fall in blood pressure of 35 mm Hg, but the same amounts of sodium diatrizoate and sodium diprotrizoate caused falls of only 10 and 15 mm Hg, respectively. That the lesser responses to sodium diatrizoate and sodium diprotrizoate were not due to impaired reactivity after the first angiography with sodium acetrizoate is evident from the fact that on further injection of 0.2 ml sodium acetrizoate (No. 4 in the figure) the response was largely unchanged, the blood pressure falling by 30 mm Hg.

Another typical experiment is illustrated in Fig. 3. Injection of 0.1 ml sodium acetrizoate into the common carotid artery promptly reduced the blood pressure by 25 mm Hg. The heart rate at the same time decreased from 230 to 130 beats per minute, *i. e.* by no less than 43 per cent. (In this experiment, as in the others, the lowest rate — in this instance 130 beats per minute — was calculated as the average of the five slowest beats.) The effect was of fairly short duration: a normal blood pressure level and heart rate were reached within one minute and half a minute respectively. The corresponding values after the sodium diatrizoate injection 15 minutes later were a fall in blood pressure of 10 mm Hg and a heart rate of 195 beats per minute, a decrease of 15 per cent. An almost complete return to normal had already occurred after 15 seconds.

The mean values from all experiments are set forth in Fig. 4. From this it is evident that as regards the biologic activity of the contrast media upon autonomic structures in the brain, of which the relevant circulatory phenomena should be considered a result, according to LINDGREN and TÖRNELL (1958) (11), there is a difference between the monoamino compound sodium acetrizoate on the one hand and the diamino compounds sodium diatrizoate and sodium diprotrizoate on the other.

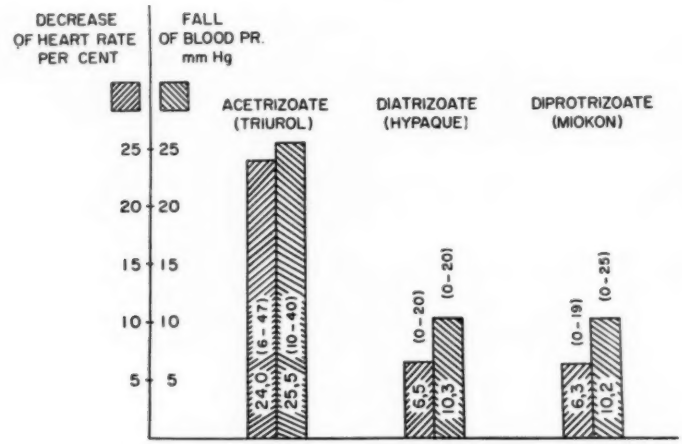


Fig. 4. Decrease of heart rate and fall of blood pressure on injection of contrast media (0.1 to 0.4 ml) into the common carotid artery. Mean values from 12 experiments (sodium diprotrizoate only 7 experiments).

Discussion

Since the doses employed were relatively small — usually less than 0.1 ml per kg body weight, and hence of the same order of magnitude as in carotid angiography in man — it does not appear unreasonable to make certain comparisons between the present results and those reported in studies in human beings. Yet it must be borne in mind that the carotid anatomy in the cat differs greatly from its human counterpart, and also varies in different cats. For this latter reason the amount of contrast medium that will reach a certain cerebral structure in the individual case may vary considerably, a fact that may be one reason for the absence of any response in a few cases and a wide range of values in the remainder. This and allied problems are discussed in more detail in papers by KÅGSTRÖM et coll. and LINDGREN and TÖRNELL (11). It should also be pointed out that due to the anatomical relations the great bulk of the contrast medium injected into the common carotid artery will have an extracerebral distribution.

As regards the nature of the circulatory effects, hypotension and bradycardia, in carotid angiography with sodium acetrizoate, the findings closely accord with GREITZ' observations. It seems likely that the effects are due to a direct action on autonomic centers in the brain; for their detailed mechanism as well as the possible significance of carotid sinus reflexes, reference should be made to the just mentioned paper by LINDGREN and TÖRNELL.

LINDNER et coll. reported having observed 'temporary slowing of th pulse' on injection of sodium diatrizoate into the carotid artery in do s. In the description of their method they mention having varied th amount, concentration, and rate of injection; but in their presentatio n of the results, which gives no quantitative data, nothing is said ab ut those factors. Possibly they administered 20 ml sodium diatrizoate 50 % which — experimentally as well as clinically — represents an exces ively large dose; a similar response was observed after sodium acetri oate (Urokon). It thus seems difficult to compare their results with th present ones.

The difference in activity between the monoamino compound, sodium ace trizoate, on the one hand, and the diamino compounds diatrizoate and diprotrizoate, on the other, is interesting in view of clinical reports on comparisons of the various agents. BROADBRIDGE, as mentioned earlier, reported that sodium diatrizoate produced fewer side-effects in forms of a sensation of heat and subjective distress than did sodium acetrizoate. SMOLIK and NASH found no significant changes of blood pressure or heart rate during carotid angiography in human subjects with Hypaque (50 %, 12 ml per injection). The distinct difference in depressor and bradycardiac effect between the acetrizoate and diatrizoate compounds that was found in the present investigation has also been verified in human subjects by SJÖGREN. The writer is not aware of any similar comparison with sodium diprotrizoate.

From the clinical standpoint, even a moderate fall in blood pressure and moderate bradycardia are undesirable side-effects insofar as they may serve to prolong the duration of contact of the contrast medium with the cerebral vascular endothelium (in the following termed 'application time'). The dangers of increased vascular permeability and damaged blood-brain barrier have been emphasized by BROMAN and OLSSON (5) and BROMAN, FORSSMAN and OLSSON (3), among others. Yet it is difficult to judge whether in this case a prolonged application time should actually be expected in angiography with any of the three contrast media used in this investigation, especially the sodium acetrizoate. Any retardation of the cerebral circulation due to causes we have mentioned would be unlikely to precede the declining phase of the blood pressure and heart rate response. The response has a latency of about two seconds, and bradycardia is most marked after 3 to 8 seconds. HOLM, and GREITZ give circulation times through the brain (man) of 3.25 and 2.7 to 5.5 seconds respectively, STEWART, and WOLFF and BLUMGART corresponding times of 3.4 and 3 seconds respectively in cats. Hence a large proportion of the contrast medium should have left the brain before the response reaches its maximum. Yet in marked responses with a short latent period, extreme

bradycardia and long duration, the application time may be lengthened, possibly resulting in toxic effects.

Another complicating factor in evaluation of the cerebral circulation during carotid angiography is the direct vascular effect of the contrast medium. Sodium acetrizoate, as shown by KÅGSTRÖM et coll., causes vasodilatation with an increase of 100 to 300 per cent in the cerebral blood flow. This elevation of the flow begins, however, after about 10 seconds and thus is unlikely to influence appreciably the application time.

Bearing in mind that these effects on the systemic circulation during carotid angiography (11) are probably attributable to a direct action of the contrast medium on nervous structures, it is interesting to consider the present results in relation to what is known about the effects of the various contrast media on the vascular permeability and the blood-brain barrier. If the permeability is greatly affected, there may be increased passage of contrast substance through the vessel walls. WHITELEATHER and DESAUSURE in 1956, using a method similar to that reported by BROMAN and OLSSON in 1948, compared sodium diatrizoate with sodium acetrizoate in dogs, and observed that the latter contrast medium caused far greater damage to the blood-brain barrier. In a few cases they also studied sodium diprotrizoate, which on the whole was found to be just as indifferent as sodium diatrizoate. Similar results with regard to sodium diatrizoate and sodium acetrizoate in dogs were reported by LINDNER et coll. However, both these groups of authors used fairly large amounts of contrast medium, and it is possible that sodium acetrizoate in smaller amounts would not affect the permeability to any appreciable degree. BROMAN and OLSSON found in rabbits relatively little disturbances of permeability with that contrast medium (Triurol), at least in low concentration. It nevertheless seems clear that a difference exists in this respect between sodium acetrizoate on the one hand and sodium diatrizoate and sodium diprotrizoate on the other. A similar difference in the pulse and blood pressure responses was demonstrated in the present investigation. It does not appear possible to decide whether this consistency should be taken to imply that the relevant nervous effects are promoted or are caused by disturbances of vascular permeability.

Acknowledgement

This investigation was supported by a grant from the Swedish Medical Research Council, which is gratefully acknowledged.

SUMMARY

Blood pressure and heart rate were recorded in cats during injections into the common carotid artery of small doses (0.1 to 0.4 ml) of contrast media of the tri-iodobenzoic acid type: sodium acetrizoate (Triurol), sodium diatrizoate (Hypaque), and sodium diprotrizoate (Miokon). Some clinical implications of the experimental findings are discussed, and the difference in action on the pulse and blood pressure is compared with other known differences between the three contrast media in their pharmacologic effects, e.g. on the blood-brain barrier.

ZUSAMMENFASSUNG

Der Blutdruck und die Herztätigkeit wurden bei Katzen während der Injektion kleiner Dosen (0.1 bis 0.4 ml) von Kontrastmitteln vom Typus der Trijodbenzoesäure, nämlich des Natriumazetrizoat (Triurol), des Natriumdiatrizoat (Hypaque) und des Natriumdiprotrizoat (Miokon) in die Arteria carotis communis registriert. Einige klinische Beziehungen der experimentellen Befunde werden besprochen. Die Unterschiede in der Wirkungsweise auf den Puls und den Blutdruck werden mit anderen bekannten Differenzen zwischen den 3 Kontrastmitteln bezüglich ihres pharmakologischen Effektes, d. h. auf die Blut-Hirnbarriere, verglichen.

RÉSUMÉ

La pression sanguine et le rythme cardiaque ont été enregistrés sur des chats, pendant l'injection dans la carotide primitive de petites doses (0.1 à 0.4 ml) de moyens de contraste du type acide triiodobenzoïque: acétrizoate de sodium (Triurol), diatrizoate de sodium (Hypaque) et diprotrizoate de sodium (Miokon). L'auteur examine quelques-unes des conséquences cliniques de ces résultats expérimentaux et compare les différences d'action de ces trois moyens de contraste sur le pouls et sur la pression sanguine avec d'autres différences connues dans leurs effets pharmacodynamiques, par exemple sur la barrière hémo-cérébrale.

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DIVERGENCE OF A RESTRICTED BUNDLE OF ROENTGEN RAYS

by

Pekka Vuorinen

The author has examined certain elementary roentgengeometric facts in connection with another investigation and believes that this study may be of some general interest.

The starting points were the roentgenographic methods based on the use of a narrow beam of roentgen rays (1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 14, 15, 16, 17, 18) in the aim to obtain an orthoroentgenographic (1, 3, 5, 7, 9, 10, 11, 14, 16), tomographic (6, 9, 12, 15, 17, 18), or some other special effect (2, 11). It is common to all these methods that during the exposure the roentgen bundle and the object are moving in relation to each other. The breadth and the divergence of the roentgen bundle therefore have a very remarkable effect on the distinctness of the roentgenographic image. This is illustrated by the example in Diagram 1. Supposing the film and the object be static and the roentgen tube moving during the exposure, it can be seen that when the tube is in position *F1*, one edge of the (diverging) roentgen ray bundle will run through point *P* to point *P1* in the film. As the bundle of rays is moving, point *P* is recorded in the film until the other edge of the bundle runs through *P* to point *P2* in the film. Distance *P1—P2* represents the blurring of the image of point *P;* the smaller the divergence of rays, the smaller the blurring.

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This example cannot as such be applied to all the methods mentioned above; its only purpose is to give a general idea of the significance of the divergence in slit methods. It has not yet been possible to produce parallel roentgen rays, although theoretical suggestions for doing so have been made (8, 13).

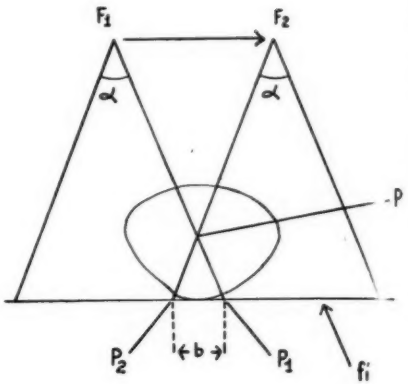

Diagram 1. As the roentgen tube moves from *F1* to *F2* during the exposure and the divergence of the roentgen-ray bundle is *a*, the distance *P1 — P2* represents the blurring of the image at point *P*. b — blurring; fi — film.

A geometrical examination of the roentgen ray bundle (Diagram 2) shows that area K in the film corresponds to that part which is submitted to the roentgen rays emitted from focal spot F, when the roentgen bundle is limited by a roentgen ray absorbing plate T in which only a narrow slit (with an aperture of 'a') permits the passage of the rays. (This investigation concerns only one plane; in the plane parallel to the slit the rays are 'freely' diverging.) D is the distance of the aperture from the optically effective focal spot and H the distance between the slit and the film; distance X is an auxiliary measurement. From the figure, the following formulae are obtained:

$$\frac{a}{F} = \frac{x}{D - x}$$

and

$$\frac{K}{H + x} = \frac{a}{x}$$

From these

$$K = \frac{H\ (F + a)}{D} + a \qquad (1)$$

This geometrical formula is also valid when $a < F$. By it, the breadth of the bundle of rays at a known distance is expressed. In practice, however, it is usually more convenient to use half of the divergence angle or its tangent (4). From Diagram 2 it is seen again that

$$tg\ {}^1/_2\ \alpha = \frac{F + a}{2\ D} \qquad (2)$$

At small angles,

$$tg\ {}^1/_2\ \alpha = {}^1/_2\ \alpha \text{ (radian)}$$

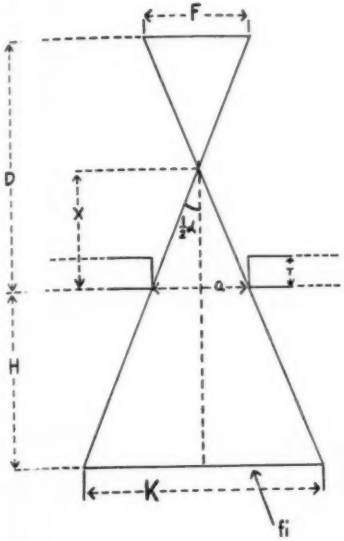

Diagram 2. The breadth and the divergence of a restricted bundle of roentgen rays.

F — focal spot
D — distance from focal spot to restricting slit
H — distance from slit to film
K — breadth of roentgen-ray bundle on plane of film (fi)
T — slit plate (of lead)
$^1/_2\alpha$ — half of the divergence angle
x — distance between 'converging point' on the geometrical system and center of the lower aperture of slit

$$K = \frac{H\ (F + a)}{D} + a \quad \text{and} \quad tg\ ^1/_2\,\alpha = \frac{F + a}{2\ D}$$

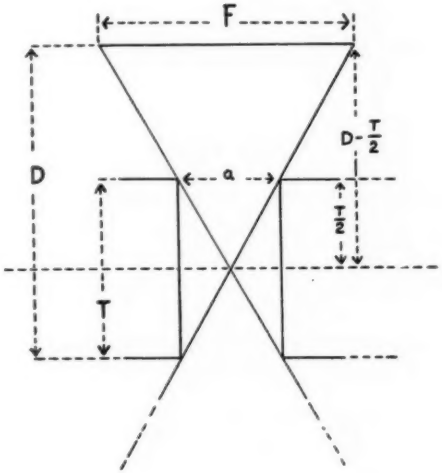

Diagram 3. As the thickness of the slit plate (T) becomes great in relation to the aperture (a) of the slit, the upper edges of the slit begin to restrict the breadth of the roentgen-ray bundle. F — size of the focal spot, D — distance between the focal spot and the lower aperture of the slit.

Table

The breadth of the roentgen-ray bundle (K) at a distance of 1400 mm from the focal spot (F), with focal sizes of 0.3, 1.2, 2.0 and 3.0 mm, when the aperture of the slit (a) varies from 0.05 to 100 mm, and the distance (D) from the focus to the aperture is 350 mm, and the distance (H) between the aperture and the film 1050 mm. Corresponding divergence angles and their tangents are also shown.

a mm	F = 0.300 mm			F = 1.200 mm			F = 2.000 mm			F = 3.000 mm		
	K mm	$tg\ ^1/_2\ a$	$^1/_2\ a°$	K mm	$tg\ ^1/_2\ a$	$^1/_2\ a°$	K mm	$tg\ ^1/_2\ a$	$^1/_2\ a°$	K mm	$tg\ ^1/_2\ a$	$^1/_2\ a°$
0.05	1.1	0.0005	0.03	3.8	0.0018	0.10	6.2	0.0029	0.17	9.2	0.0043	0.25
0.1	1.3	0.0006	0.03	4.0	0.0019	0.11	6.4	0.0030	0.17	9.4	0.0044	0.25
0.2	1.7	0.0007	0.04	4.4	0.0020	0.12	6.8	0.0031	0.18	9.8	0.0046	0.26
0.3	2.1	0.0009	0.05	4.8	0.0021	0.12	7.2	0.0033	0.19	10.2	0.0047	0.27
0.5	2.9	0.0011	0.06	5.6	0.0024	0.14	8.0	0.0036	0.21	11.0	0.0050	0.29
0.8	4.1	0.0016	0.09	6.8	0.0028	0.16	9.2	0.0040	0.23	12.2	0.0054	0.31
1.0	4.9	0.0019	0.11	7.6	0.0031	0.18	10.0	0.0043	0.25	13.0	0.0057	0.33
1.5	6.9	0.0026	0.15	9.6	0.0038	0.22	12.0	0.0050	0.29	15.0	0.0064	0.37
2.0	8.9	0.0033	0.19	11.6	0.0046	0.26	14.0	0.0057	0.33	17.0	0.0071	0.41
2.5	10.9	0.0040	0.23	13.6	0.0053	0.30	16.0	0.0064	0.37	19.0	0.0078	0.45
3.0	12.9	0.0047	0.27	15.6	0.0060	0.34	18.0	0.0071	0.41	21.0	0.0086	0.49
5.0	20.9	0.0076	0.44	23.6	0.0089	0.51	26.0	0.0100	0.57	29.0	0.0114	0.65
8.0	32.9	0.0118	0.67	35.6	0.0131	0.75	38.0	0.0143	0.82	41.0	0.0157	0.90
10.0	40.9	0.0147	0.84	43.6	0.0160	0.92	46.0	0.0171	0.98	49.0	0.0186	1.07
15.0	60.9	0.0219	1.26	63.6	0.0231	1.32	66.0	0.0243	1.39	69.0	0.0257	1.47
20.0	80.9	0.0290	1.66	83.6	0.0303	1.74	86.0	0.0314	1.80	89.0	0.0328	1.88
50.0	200.9	0.0719	4.11	203.6	0.0731	4.19	206.0	0.0743	4.25	209.0	0.0757	4.33
100.0	400.9	0.1433	8.16	403.6	0.1446	8.23	406.0	0.1457	8.29	409.0	0.1471	8.37

$H = 1050$
$D = 350$

$$K = \frac{H\,(F + a)}{D} + a \qquad tg\ ^1/_2\ a = \frac{F + a}{2\,D}$$

The breadth of the roentgen ray bundle (K) at a distance of 1400 mm from the focal spot is presented in the table. The sizes of the focal spots (F) used in the calculations are 0.3, 1.2, 2.0 and 3.0 mm, the distance (D) between the focus and the slit is 350 mm and the aperture (a) varies from 0.05 to 100 mm. The corresponding divergence angles (in degrees) and their tangents are also shown in the table.

If the breadth of the slit becomes very small in comparison with its thickness (T), the superior edges of the slit begin to restrict the bundle of rays (Diagram 3). This does not happen until

$$3 = \frac{F \cdot T}{2D - T} \text{ or smaller.}$$

For example, if $D = 300$ and $F = 2.0$, the upper edges of the slit begin to limit the bundle only when

$$a = 0.034 \quad \text{by} \quad T = 10.0$$
$$\text{and } a = 0.0067 \quad \text{by} \quad T = 2.0 \qquad (3)$$

To confirm these calculations, experiments were carried out with various roentgen tubes and focal spots and at various distances and apertures. It could be verified that in every instance the calculated breadth of the roentgen ray bundle was in accordance with the breadth measured in the corresponding film within the limits of measurement errors.

SUMMARY

The divergence of a restricted bundle of roentgen rays was investigated geometrically. A formula, expressing the breadth of the roentgen ray bundle at a known distance from the slit and the focal spot, is presented.

ZUSAMMENFASSUNG

Die Divergenz eines begrenzten Röntgenstrahlenbündels ist geometrisch untersucht worden. Eine Formel, welche die Breite des Röntgenstrahlenbündels in einem gewissen Abstand vom Spalt und dem Fokus angibt, wird vorgelegt.

RÉSUMÉ

L'auteur a étudié géométriquement la divergence d'un faisceau diaphragmé de rayons roentgen. Il présente une formule donnant la largeur du faisceau de rayons roentgen à une distance connue de la fente et de la tache focale.

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CANCER OF THE VULVA

Analysis of results of treatment during the years 1935—1955

by

Bent Langfeldt-Andersen

The treatment of cancer of the vulva has in the course of time confronted surgeons, gynaecologists and radiotherapists with great problems, and the results obtained have often been disappointing.

The disease is relatively rare. According to DEN HOED cancer of the vulva constitutes only 1 % of all cases of cancer of the female genital tract. The frequencies observed by ISTRE and by KÜHNELT were 7.7 and 2.2 %, respectively, while PALMER et coll. found an incidence of 3.88 % in a comprehensive series of 8,000 cases. In his textbook of gynaecology, INGERSLEV gives a figure of about 3 %.

During the years 1935—1955, a total of 4,380 cases of cancer of the female genital tract were treated in the Radium Centre for Jutland. Of these, 165 were cancers of the vulva, which gives an incidence of 3.8 %.

The therapeutic problems related to cancer of the vulva are:

1. The disease is most frequently encountered in elderly, frail patients, who stand major surgery very poorly (3, 4).

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2. Radical excision can often be performed only by an extensive and incapacitating operation (1, 6, 26, 27).

3. The genital region is a poor field for radiotherapy (10, 28).

4. The carcinomata, which are most frequent among the tumours of the vulva, are relatively radioresistant (21).

5. Owing to the anatomic conditions, metastases readily develop, often with involvement of the deep intrapelvic lymph nodes (3, 4, 21, 29, 32, 33).

6. The incidence of recurrence is high (21).

Although cancer of the vulva is, in fact, a cutaneous lesion, its special localization in a region with thin skin covering an adipose cavernous tissue renders all forms of therapy difficult; this applies, in particular, to radiation therapy, because prickle-cell carcinomata are relatively radioresistant, while comparatively low doses of irradiation administered to the tumour bed may give rise to necrosis, which is very apt to occur in regions with moisture and friction (28).

Thus, close-distance roentgen therapy, which is very effective in other skin cancers, and radium implantation (16) have proved to be inadequate in cancer of the vulva. Owing to the failure of radiotherapy, attempts have been made to elaborate effective surgical methods. Among these surgical measures may be mentioned: BERVEN's bipolar electrocoagulation, which marked a great step forward, partial or complete vulvectomy sometimes supplemented by radiotherapy, very extensive surgical intervention with removal of intrapelvic lymph nodes, and operations of varying extent of the pelvic viscera, which have been used especially in the U. S. A. during recent years.

Teleradium treatment has, however, given fairly good results, and telecobalt or high-voltage techniques may result in further advances within the field of radiotherapy.

The results of treatment have varied within wide limits. Thus, ROTHSCHILD (cited by BERVEN 3, 4) in 1912 obtained five-year cures in only 4.87 % of his cases after surgical treatment.

In his famous thèse which appeared in 1912, BASSET described a method of operation with vulvectomy and nodal dissection 'en bloc', which greatly stimulated the interest in surgical treatment of the condition. It is noteworthy that BASSET, who devised his method by detailed studies of the pathologic conditions in a series of autopsy subjects, never personally performed the operation on living individuals.

During the next 25 years or so, the rates of five-year cures were about 30 %. The publication of a study on cancer of the vulva by TAUSSIG

in 1940 was followed by a large series of analyses which showed steadily improving results, especially of purely surgical treatment, and culminated with the publication of the 'Results of a planned attack on carcinoma of the vulva' by WAY in 1954.

With intensive team work, WAY had attained five-year survivals in 61 % of all the cases in the series and in 86 % of the cases in which the lymph nodes were uninvolved.

Personal investigation

The series comprised 165 patients who were admitted to the Radium Centre with cancer of the vulva during the period 1935—1955.

Most of the patients were elderly women. Thus, only in 26 cases did the tumour develop before menopause, while it occurred in the postmenopausal age in 139 cases, or 84.2 %. The ages of the patients ranged from 19 to 88 years and averaged 62.2 years. Of the patients, 65.5 % were over 60, 33.5 % over 70, and 9.1 % over 80 years of age.

As already mentioned, prickle-cell carcinoma is the most frequent histologic finding; this variety was found in 80 % of the cases in this series (Table 1).

Table 1

Histologic diagnoses

Carcinomata		
Prickle-cell		132 = 80 %
Squamous-cell	7	
Basal-cell	6	
Papillary	1	
Incipient	1	
Adenocarcinoma	3	18
		150 = 92 %
Sarcomata		
Melanosarcoma	9 (5.5 %)	
Fibrosarcoma	1	
Spindle-cell	1	
Liposarcoma	1	12 = 7.4 %
Precancerous changes	1	
No histologic examination	2	3
Total		165

The carcinoma represented a total of 92 % and the sarcomata 7.4 % (12 patients). Nine of these 12 patients suffered from malignant melanoma (5.5 %). This is in agreement with the figures reported by JØRGSHOLM, who among 141 cases of malignant melanoma observed 9 involving the vulva.

It is a well-known fact that patients with cancer of the vulva often seek medical aid only at a relatively late stage of the disease, in many

cases presenting extensive cancers which have already given rise to metastases. In some cases, the tumour may be so large that it causes purely mechanical discomfort in walking or in the sitting position (Table 2).

Table 2

Duration of symptoms

0— 5 months	59	
6—11 »	36	
Total of less than 12 months		95
1 year	30	
2 years	7	
3 »	18	
5 »	9	
Total of more than 12 months		64 = 38.8 %
No information	6	
	In all 165	

It appears from Table 2 that 64 of the patients (38.8 %) had had their tumour for 12 months or more. In 66.7 % of the cases, it was the development of ulcerations or nodules which made the patient apply for treatment. Pruritus of the vulva was a conspicuous symptom in 23 % of the patients, and in 18.2 % it was this which caused the patient to seek treatment (Tables 3 and 4).

Leukoplakia and kraurosis, which may play a part in the development of cancer, occurred in 21.2 % of the cases, whereas syphilis was present in only 1.2 %.

Granulomatous infections, such as lymphogranuloma inguinale and condylomata acuminata, which according to GREENE and POMERANCE may predispose to cancer, did not occur in this series.

Table 3

Survey of symptoms

	Number of cases	%
Ulceration or nodules	110	66.7
Pruritus	30	18.2
Pain	30	18.2
Dysuria	27	16.4
Burning pain in vulval region	23	13.9
Patchy bleeding	18	10.9
Discomfort in walking or sitting	14	8.5

Table 4

Preceding conditions

	Number of cases	%
Syphilis	2	1.2
Diabetes mellitus	4	2.4
Leukoplakia	20	12.1
Kraurosis, vulvitis	15	9.1
Severe pruritus	38	23.0

Classification. In the classification of cancer of the vulva, many methods have been suggested. TAUSSIG used 5 stages, MCKELVEY 4 stages and LUNDWALL 4 groups.

Of the methods of classification so far used, that suggested by BERVEN seems to be the most appropriate. He divided his series into 4 groups according to the local extension of the tumour and into 3 stages according to the involvement of the lymph nodes.

His groups are as follows:

Group 1. Non-ulcerated tumour, less than 1 cm in diameter, confined to one part of the vulva, for example, the labia, clitoris or posterior commissure. The tumour is freely movable over the underlying tissue and not surrounded by any appreciable oedema.

Group 2. Tumour larger than 1 cm in diameter, often ulcerated, infected and surrounded by oedema, but still confined to one part of the vulva.

Group 3. Tumour not confined to one part of the vulva, but invading surrounding tissues (possibly with implantation metastases).

Group 4. Tumour involving the entire vulva, possibly invading the vagina, surrounding skin or perineum, or continuing directly into the inguinal region.

BERVEN's stages are as follows:

Stage I. Small movable, fairly well-defined lymph nodes of normal or slightly increased consistency.

Stage II. Enlarged, hard lymph nodes with perinodal infiltration and great probability of metastases.

Stage III. Enlarged, hard, fixed lymph nodes with very great probability of metastases.

Results of treatment. Of the 165 cases in the series, six were excluded from the analysis for the reasons stated below.

	Number of cases
Primary postoperative death from embolism of pulmonary artery	2
No treatment	
Death from mesenterial thrombosis on 2nd hospital day	1
Death from distant metastases on 4th hospital day	1
Death from general debility after 4 weeks in hospital	1
Treatment elsewhere, but followed in this hospital	1
Total	6

Of the remaining 159 patients, 138 were followed for 5 years or more. These patients were treated by one of the three following methods:

I. *Electrocoagulation:* in some cases, supplemented by radiotherapy or nodal dissection.

II. *Surgical treatment:* usually, partial or complete vulvectomy, dissection of inguinal lymph nodes and, in most cases, postoperative radiotherapy.

III. *Radiotherapy:* in some cases, supplemented by electrocoagulation.

Table 5

Results of treatment distributed according to groups and stages (BERVEN)

	Group				Unclassifiable	Stage			Unclassifiable	Total
	1	2	3	4		I	II	III		
Electrocoagulation:										
Deaths	1	25	17	1	0	33	3	7	1	44
Recurrence	0	4	2	0	0	6	0	0	0	6
No symptoms	1	8	7	0	0	14	2	0	0	16
Total	2	37	26	1	0	53	5	7	1	66
Surgical treatment:										
Deaths	1	24	5	1	1	24	2	6	0	32
Recurrence	0	1	0	0	0	1	0	0	0	1
No symptoms	3	9	1	1	1	11	2	1	1	15
Total	4	34	6	2	2	36	4	7	1	48
Radiotherapy:										
Deaths	0	3	12	8	0	8	3	11	1	23
Recurrence	0	0	0	0	0	0	0	0	0	0
No symptoms	0	0	1	0	0	1	0	0	0	1
Total	0	3	13	8	0	9	3	11	1	24
Grand total	6	74	45	11	2	98	12	25	3	138

Table 6

Over-all results of treatment in 138 cases followed for at least 5 years

	Deaths	Recurrence	Freedom from symptoms Numbers	Freedom from symptoms %	Total
Electrocoagulation	44	6	16	24.2	66
Surgical treatment	32	1	15	31.3	48
Radiotherapy	23	0	1	4.1	24
Total	99	7	32		138

The results obtained by the three forms of treatment are shown in Table 5, distributed according to groups and stages (BERVEN), and in Table 6, which gives the over-all results.

It appears from Table 6 that a five-year survival without recurrence was obtained in 24.2 % of the patients treated with electrocoagulation.

in 11.3 % of those subjected to surgical treatment, but only in 4.1 % of the cases in which radiotherapy was given.

If the last group is left out of account, the average five-year survival rate is 27.8 %, which is in agreement with the results reported from Norsk Radiumhospital by ISTRE in 1951. The results of surgical treatment are somewhat better than those obtained by electrocoagulation, but inferior to those reported from some surgical and gynaecologic clinics in the U. S. A. and England during recent years.

However, it must be borne in mind that our series comprised a relatively large number of severe cases, while patients with small, readily accessible tumours are treated in other surgical or gynaecologic clinics. Moreover, the series covers a period of 20 years, during which the principles of treatment varied within wide limits; surgical treatment has particularly been employed during recent years, in which great developments have occurred in the administration of anaesthesia and blood transfusions.

It appears that radiotherapy alone, or followed by electrocoagulation, gives relatively poor results. This treatment was, in fact, used almost exclusively in old patients in a poor general condition with extensive tumours. This appears from Table 7, in which it is seen that not less than 58.3 % of the patients who received radiotherapy almost certainly had inguinal metastases.

Table 7

Distribution, in percentage, according to involvement of inguinal lymph nodes

Stage	II	III	II + III
Electrocoagulation	7.6 %	10.6 %	18.2 %
Surgical treatment	8.3 %	14.6 %	22.9 %
Radiotherapy	12.5 %	45.8 %	58.3 %

As already pointed out, our attitude to surgical treatment during recent years has become more active. A separate analysis of the results obtained in patients treated during the years 1948—1955, *i. e.* patients with an observation period of at least 3 years, shows that the percentage of cure has risen to 43.8 % (Table 8).

Table 8

Results obtained in 59 cases treated during 1948—1955

	Deaths	Recurrence	Freedom from symptoms Numbers	%	Total
Electrocoagulation	18	3	11	34.4	32
Surgical treatment	9	0	7	43.8	16
Radiotherapy	9	0	2	18.2	11
Total	36	3	20		59

Conclusions

In view of the developments which have occurred within the fields of surgery and anaesthesiology during the last 20 years, it can scarcely be doubted that surgical treatment with vulvectomy — in particular complete vulvectomy with nodal dissection — is the method of choice in cancer of the vulva, whereas electrocoagulation is a useful procedure in the presence of very small tumours or more extensive superficial tumours. In such cases, bipolar electrocoagulation by the method of BERVEN gives good results, and should not be allowed to pass into oblivion.

Radiotherapy alone does not cure the primary tumour and is, accordingly, indicated only when the principal aim of treatment is palliation.

SUMMARY

The results of treatment obtained during the period 1935—1955 in a series of 165 cases with cancer of the vulva are presented, the principal method of treatment being electrocoagulation, surgical treatment or radiotherapy. A total of 138 cases were followed for at least 5 years. Five-year survival was obtained in 24.2 % of the cases treated with electrocoagulation, in 31.3 % of those subjected to surgical treatment, but only in 4.1 of the cases in which radiotherapy was employed. For a group of 59 cases treated during 1948—1955 the corresponding three-year survival rates were 34.4 %, 43.8 % and 18.2 %.

ZUSAMMENFASSUNG

Die Behandlungsresultate von 165 Vulvakarzinomen, die während der Jahre 1935—1955 erzielt worden sind, werden vorgelegt. Die wesentlichsten Behandlungsmethoden waren Elektrokoagulation, Chirurgie und Radiotherapie. Insgesamt 138 Fälle sind mindestens 5 Jahre lang beobachtet worden. Von den mit Elektrokoagulation behandelten Fällen hatten 24.2 % eine Überlebenszeit von 5 Jahren; die chirurgisch behandelten Fälle erreichten 31.3 %. Die radiologisch behandelten Fälle zeigten jedoch eine 5-Jahre-Überlebenszeit von nur 4.1 %. Für eine Gruppe von 59 Fällen, die während der Jahre 1948—1955 behandelt worden sind, waren die entsprechenden Prozentzahlen für die 3-Jahre-Überlebenszeit 34.4 %, 43.8 % und 18.2 %.

RÉSUMÉ

L'auteur présente les résultats thérapeutiques obtenus au cours de la période 1935—1955 sur une série de 165 cas de cancer de la vulve; la méthode principale de traitement a été l'électrocoagulation, le traitement chirurgical ou la radiothérapie. 138 cas au total ont été suivis pendant au moins 5 ans. Une survie de cinq ans a été obtenue dans 24.2 % des cas traités par électrocoagulation; dans 31.3 % des cas opérés, mais dans seulement 4.1 % des cas traités par radiothérapie. Pour un groupe de 59 cas traités entre 1948 et 1955, les taux de survie de trois ans correspondants sont 34.4 %, 43.8 % et 18.2 %.

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CHEMICAL PROTECTION OF THE MOUSE AGAINST LEUKEMIA INDUCTION BY ROENTGEN RAYS

by

A. C. Upton, D. G. Doherty and *G. S. Melville Jr.*

A major goal of the radiobiologist is the control of radiosensitivity. Encouraging progress toward this end has been made with the synthesis of mercaptoethylguanidine (MEG), a compound which enables mice to survive otherwise lethal roentgen doses (14). To ascertain whether this chemical protects against induction of leukemia by irradiation, mice were pretreated with the drug, then given graded sublethal doses of roentgen rays. The incidence of leukemia in these animals was compared with that in similarly irradiated mice treated with saline placebos.

Methods. Male mice of the RF strain aged 5 to 6 weeks were randomly divided into two groups. One group received intraperitoneally 9.0 mg of freshly prepared MEG dissolved in 0.3 ml of 0.4 M phosphate buffer at pH 7.0, and the other group received an equal volume of physiological saline solution by the same route. About 15 minutes after injection, the animals were exposed to whole-body 250 kV roentgen rays under conditions identical to those described previously (16) (Table 1). After irradiation, the mice, all of which survived at least 120 days, were caged in groups of 10 and observed until natural death. Post mortem examinations were performed on every animal, and histologic studies were made when necessary for diagnostic purposes.

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Table 1

Effects of MEG pretreatment on leukemia-induction by roentgen rays

Roentgen dose	Pretreatment	No. of mice	Mean survival time, months	Leukemia incidence, %	
				Granulocytic	Thymic lymphoma
0	Saline	69	19.6	4.4	4.4
0	MEG	43	20.0	6.9	2.3
150	Saline	50	16.9	26.0	6.0
150	MEG	68	18.4	19.1	7.4
300	Saline	59	14.2	40.7	20.3
300	MEG	59	15.0	35.6	6.8

Results and Discussion

In the placebo-treated mice, the incidence of thymic lymphoma and granulocytic leukemia was increased by irradiation (Table 1), in accordance with the results of earlier studies (17). In the MEG-treated mice, however, the induction of granulocytic leukemia was less pronounced at both dose levels, and the induction of thymic lymphoma was completely inhibited (Fig. 1). Another noteworthy difference between the two irradiated groups was the longer survival of the MEG-treated mice. In the nonirradiated controls, MEG did not materially affect the survival or spontaneous development of neoplasms.

It was anticipated that MEG would reduce sensitivity to leukemia-induction in view of the protection it affords marrow cells against acute radiation injury in vivo (18) and in vitro (15) and because of the importance of marrow injury in the induction of lymphoma (7) and granulocytic leukemia (17). That it should be especially effective in protecting against leukemia-induction was also suggested by the relatively high selective concentration of the drug in marrow and lymphoid cells, as judged from preliminary studies of the organ distribution of S^{35}-labeled MEG (F. P. Conte, G. S. Melville, Jr., E. E. Schwartz, D. G. Doherty, and R. Shapira, 1958, unpublished data).

Although the observed protection against leukemia-induction and life-shortening is not statistically significant because of the relatively few animals used, the results are in accord with those of earlier studies indicating protection by MEG against leukemogenesis and life-shortening in irradiated mice of the (101 × C3H)F_1 strain (3). A quantitative assessment of the extent of protection against leukemogenesis must, however, await studies with additional dose levels and larger numbers of animals. In comparison, for protection against 30-day lethality (14) and bone marrow depression (18), MEG appears to reduce the effectiveness of roentgen rays by a factor of ~ 2.0.

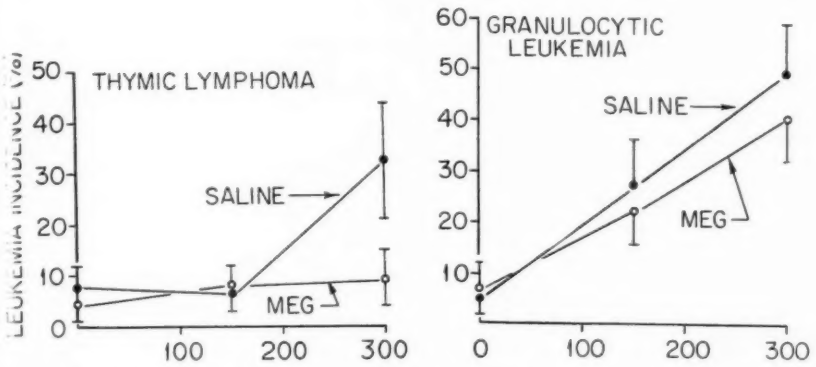

Fig. 1. Leukemia incidence in relation to roentgen dose in MEG- and saline-treated mice. The values shown, with their standard errors, represent the observed incidence after adjustment by the method of KIMBALL (8) to correct for intercurrent mortality from diseases other than leukemia.

Our results, like those of our earlier experiments (Table 2) and those of HOLLCROFT et coll. (5) indicate the feasibility of protecting animals against delayed radiation injury, as well as against acute lethality, by measures which may be applied before irradiation. Although preliminary clinical tests suggest that MEG may be too toxic for man to be of value in human protection, related agents have been synthesized that appear more promising for clinical use (D. G. DOHERTY, 1958, unpublished data).

The mechanism whereby MEG protects cells against the effects of ionizing radiation is not yet known. It is thought, however, that the major action of the drug is that of a radical-trapping agent within the cell (14). It is noteworthy that MEG also protects against the effects of nitrogen mustard (13).

Since the protective action of MEG is believed to be similar to that of cysteamine, it is paradoxical that the latter compound was not found to protect C57BL mice against induction of lymphomas by γ rays (11). In the latter case, however, the radiation was given in two exposures 5 days apart; hence, in view of the complex interaction between dose, time, and radiation intensity in lymphoma-induction (6, 12), the dose-reducing action of cysteamine and cystamine might have modified the relation between dose and interval in such a way as to enhance, rather than reduce, the leukemogenic effectiveness of the radiation.

Other reports concerning the effects of radioprotective chemicals on radiocarcinogenesis are also difficult to evaluate. For example, DUPLAN (2) failed to note protection by polyphenol derivatives against lymphoma-induction in strain XVII mice; however, his observed leukemia incidence

Table 2

Longevity and leukemia in irradiated (101 × C3H)F_1 mice treated with MEG and bone marrow [1]

Roentgen dose, r	Treatment [2]	Surviving 30 days		Median after survival [3] months	Life-shortening %/r	Leukemia (thymic lymphoma) %
		No.	%			
0	Control	110	100	25.5	0	0.09
700— 800	None	116	58	15.5	0.052	5.2
1100—1200	Bone marrow ...	113	47	13.0	0.043	0
1300—1400	MEG	134	52	13.0	0.036	0.7
1600—1800	MEG, bone marrow	110	43	12.0	0.031	0

[1] From COSGROVE, UPTON, CONGDON, DOHERTY, and KIMBALL, unpublished data, modified from HOLLAENDER et coll. (3).

[2] MEG, 8.8 mg per mouse, administered intraperitoneally 10 min before irradiation. Isologous bone marrow cells, 1 femur-equivalent in Tyrode's solution, administered intravenously immediately after irradiation.

[3] Mice were females, irradiated when 3 months old.

was lower in nonprotected mice exposed to 600 r than in those exposed to 400 r, suggesting that the frequency of leukemia was inversely related to dose in this range. Hence the slightly higher incidence of leukemia observed in his treated mice may conceivably denote dose-reduction. Without further dose-response data, his results cannot be interpreted, nor will they be meaningful until verified statistically with larger numbers of animals. Similarly, preliminary data on the occurrence of radiation-induced neoplasms in rats treated with mercaptoethylamine (10), para-aminopropriophenone (1), and hypoxia (9) cannot be evaluated for evidence of dose-reduction without additional dose-response data from nonprotected irradiated controls and without allowances for differences in longevity between the various treatment groups.

In summary, the general effectiveness of radioprotective chemicals in inhibiting radiocarcinogenesis cannot be ascertained without considerably more information than is now available. Among the facts needed for a proper evaluation of this question are more complete data on the pharmacology, metabolism, anatomic distribution, and mode of action of the various radioprotective agents. For example, cysteamine, which decreases the yield of mutations in certain bacteria (4), increases their frequency in irradiated *Neurospora* (KÖLMARK 1958, personal communication). Because of differences such as this, generalizations about protective efficacy cannot be made. It is to be hoped, therefore, that research on the action of radioprotective chemicals in cells and animals of diverse types will be intensified and that greater emphasis will be placed on their protective effects against cancer-induction and delayed radiation injury.

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SUMMARY

Administration of mercaptoethylguanidine shortly before a single whole-body exposure to 150 or 300 r of roentgen rays inhibits the induction of granulocytic leukemia and prevents the induction of thymic lymphoma in RF mice. Mice treated with the drug also exhibit less shortening of the life span by irradiation than do untreated controls.

ZUSAMMENFASSUNG

Administration von Merkapto-ethyl-guanidin kurz vor einer einzeitigen Totalbestrahlung mit 150 r bis 300 r Röntgenstrahlung inhibiert die Induktion einer Granulozytenleukämie und verhindert die Induktion eines Thymuslymphomes bei RF-Mäusen. Mäuse, die mit der Droge behandelt sind, weisen auch eine geringere Abkürzung ihrer Überlebenszeit nach Bestrahlung als unbehandelte Tiere auf.

RÉSUMÉ

L'administration de mercaptoethylguanidine peu de temps avant une irradiation unique de tout le corps par 150 ou 300 r de rayons roentgen inhibe l'induction de leucémie granulocytaire et empêche l'induction de lymphome thymique chez les souris RF. Les souris traitées par ce produit ont une durée de survie après irradiation plus longue que les témoins non traités.

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PROTON MAGNETIC RESONANCE STUDIES OF SOME TISSUES AND FLUIDS OF THE EYE

by

Arne Huggert and *Erik Odeblad*

When a sample is placed in a strong magnetic field those atomic nuclei having a spin angular momentum greater than zero will take up certain allowed orientations. The quantum theory predicts that a nucleus having a spin of I can take up one of $(2I + 1)$ permitted orientations in the magnetic field. The common (or light) hydrogen nucleus has a spin of $^1/_2$ and therefore each such hydrogen nucleus (proton) will take up one of two allowed orientations if a sample containing hydrogen in some chemical form is placed between the poles of a magnet. The upper one of these two energy levels possesses somewhat higher energy. Transitions between the two permitted states of orientation will occur if the sample is subjected to electromagnetic radiation with a frequency of 21 Mc/sec in a magnetic field of about 5,000 gauss. If the radiation frequency is kept constant, and the magnetic field is gradually varied, a nuclear magnetic resonance will be noted just as the field passes 5,000 gauss. The resonance is due to absorption of energy from the electromagnetic radiation field; this field is most easily produced in the coil of a tuned electric circuit.

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Table 1

Specimen	No of samples	Width c/sec	T_1 sec growth	T_2 sec width	T_2 sec wiggl.	Width c/sec sat.	Water %	Fr e pe t c
H_2O	7	1.5—3	3	—	0.4	6	100	10
Aq. humour	7	2—3	3	—	0.4	15—20	99	10
Corp. vitr.	18	5 (2—6)	1—3	—	0.3	6—15	99	10
Retina	4	2—3	1	—	—	10—15	89	10
Cornea	11	15 (15—20)	0.3—0.4	10.10^{-3}	—	40	75—80	8
Cortex lentis	25	15 (10—25)	0.2—0.4	10.10^{-3}	—	20—30	65—75	8
Optic nerve	6	10 (8—15)	0.1	15.10^{-3}	—	30	70	2
Ext. muscle	3	10 (7—12)	0.3—0.6	15.10^{-3}	—	35	65	—
Lacr. gland	8	10 (4—20)	0.3—0.6	15.10^{-3}	—	30—50	—	—
Sclera	11	20 (15—40)	0.1[1]	8.10^{-3}	—	60	65	8
Nucl. lentis	20	30 (10—50)	0.1[1]	5.10^{-3}	—	50—65	50—60	8

[1] Same result by saturation method.

The electronic shells shield the atomic nuclei from the bulk magnetic field. This shielding varies with the chemical structure so that a 'chemical shift' occurs between resonances of non-equivalent protons.

According to the Boltzman statistics there is a small excess population in the lower of the two energy states, and this slight excess makes net absorption of radiofrequency radiation possible. If this small excess is completely removed by strong radiation of energy from the coil so that both energy levels become equally populated, no more absorption can occur and no signal will be observed. Such a 'saturated' condition does not last for a very long time as some of the nuclei in the higher energy state loose energy to the surroundings (the lattice) and return to the lower energy state. This is the process of thermal relaxation which is characterized by a time constant, the so-named spin-lattice relaxation time or longitudinal relaxation time (T_1). (See further ANDREW's monograph.)

An exchange of energy between two nuclei also occurs so that one spin flips down at the same moment as the other flips up. This process is also characterized by a time constant, the spin-spin interaction time, or transverse relaxation time (T_2). In liquids, T_1 and T_2 are believed to be of comparable size, while in solids T_1 is much greater than T_2 (BLOEMBERGEN, PURCELL and POUND 1948).

Present investigation

Among biological materials the tissues of the eye have very special properties, one of which is the transparency for light. The physical properties and chemical structure of these parts of the eye (cornea, aqueous humour, lens and corpus vitreum) are therefore of great importance, and we considered it of interest to carry out a proton magnetic resonance study of these tissues. We also selected other tissues for study, these including the sclera, lacrimal glands, optic nerve, eye muscles and retina.

The proton magnetic resonance method primarily gives information about the nature of the water in the tissues, because water is their main component. The water present in tissues has, however, a different structure than 'free' water because of the presence of electrolytes and macromolecules of different kinds (proteins, mucopolysaccharides, etc.) capable of binding water molecules to their surfaces. The total water content in different parts of the eye varies within wide limits. The average values (NORDMANN 1954) are given in Table 1. As it is of special interest to know how large a fraction of the water is protein-bound, the values for 'free' water given by FISCHER in 1938 are also included in the same table.

Experimental. The experimental arrangement used was that described by LINDSTRÖM and BHAR (1955) with minor modifications to obtain a better resolution (about $1 : 10^7$) and enable an easy exchange of the rotating samples. A crystal-controlled oscillator generated the frequency of 21 Mc/sec, which fed the radio-frequency bridge (of double T-type). The outgoing signal from the bridge passed to a low-noise preamplifier and then to a high-gain receiver (National HRO-50). The output from the audiofrequency step of this receiver was fed to a magnetic pen motor writer (Brush Development Co).

The magnetic field, of 4,930 gauss, of the permanent magnet was swept with the aid of a generator (constructed by our technician BERTIL JOHANSSON). The sweep rate was in most cases about 0.4 ppm/sec or 8 cycles/sec^2, or 2 milligauss/sec and was varied for different purposes. The uncertainty in the sweep-rate amounted to about 10 per cent.

The experimental arrangement provided the possibility of rotating the sample and of obtaining a field average according to the mechanism proposed by BLOCH 1954 and ANDERSON and ARNOLD 1954, and discussed in detail by WILLIAMS and GUTOWSKY 1956.

About 20 mm^3 of material were introduced into a sample tube. This had an outer diameter of about 2.2 mm and an inner diameter of about 2.0 mm. A small very thin-walled tube with a diameter of about 0.5 mm

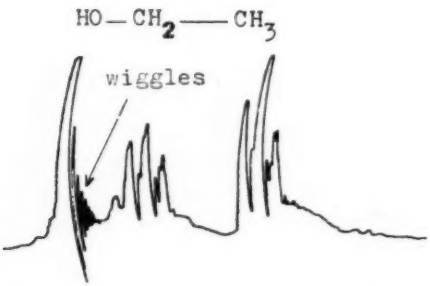

Fig. 1. Proton resonance spectrum of ethyl alcohol showing the resolution and scale. 'Wiggles' appearing after the hydroxyl resonance indicate that the resolution is better than 0.15 ppm. The distance between OH and CH_3 (central peak) is 4.3 ppm.

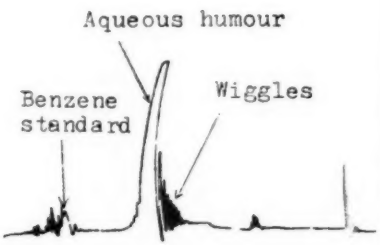

Fig. 2. Proton resonance spectrum of aqueous humour showing narrow resonance peak with 'wiggles'. The decay rate of wiggles indicate that T_2 is more than 0.5 sec. Benzene standard is localized 1.8 ppm from the signal of the sample.

containing a reference standard was introduced centrally into the sample. Water, benzene or paraffin oil (30 centipoises) were used as reference standards. Benzene gives a satisfactory calibration of the position of the signal of the sample and paraffin oil makes it possible to measure the size and position of the signal after saturation; water was used as a reference standard in a few cases.

The sample was introduced into the spectrometer in a carefully controlled position. Tuning of the receiver to the oscillator frequency and careful balancing of the bridge were performed so that a pure absorption signal was obtained. Two to four acceptable signals were recorded. If the records did not show satisfactory agreement, tuning and balancing were repeated.

The time constant of the magnetic pen motor was short (about 0.05 sec) so that the records were free from inertial artefacts. The recorder had a nearly linear response.

The spin-lattice relaxation time was determined either by direct observation of signal growth after saturation, or by comparing the size of the signals obtained from the sample and paraffin oil at saturation. When the first method was used the resonance condition was passed slowly until saturation occurred; the nuclear magnetization was then observed by a rapid passage backwards through resonance. This method was employed in the range 0.1 to 10 sec. The other method was mainly used to obtain information on short relaxation times, 0.1 sec or shorter; in this case the resonance signals were passed slowly and the signal area was compared with that of the standard.

T_2 was calculated from the line width in those cases where the signal was broader than the resolution width. One may, however, recall that

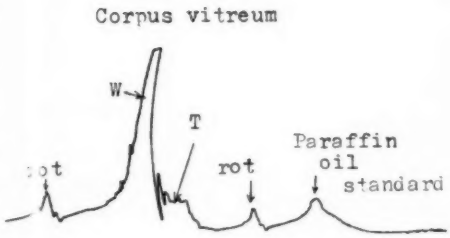

Fig. 3. Spectrum of corpus vitreum with paraffin oil standard. The distance between the signal of the sample and the oil standard is in this case 4.2 ppm. The peaks denoted 'rot' arise from the rotation of the sample and occur symmetrically on each side of the main signal W. The signal from the corpus vitreum consists of two components W and T (notations are the same as in the paper by ODEBLAD and WESTIN (1958).

if the signal consists of unresolved peaks confluencing to a broad signal the value of T_2 will be erroneously low. In cases of long spin-spin interaction times 'wiggles' occurred and their decay rate gave the minimum value for T_2.

Results and Discussion

The experimental values are collected in Table 1. We have not found any change of position within the experimental errors (about $\pm$ 0.3 ppm for a single determination). The line widths in cycles/sec are given in the columns 2 and 6; the range found is included within brackets.

Some typical signals are exemplified in Figs. 1 to 5.

It appears from Table 1 that the decrease in water content may be correlated to the increase in line width and with the decrease in T_1 and T_2. It was, however, very difficult to introduce some of the samples into the test tubes, and loss of tissue water may therefore have occurred during the preparation of the samples. This source of error has been especially difficult to avoid for samples of the lens nucleus.

The decrease in T_1 is probably related to the increase in intrinsic viscosity with decrease in water content. The presence of paramagnetic compounds in the tissues will also produce a decrease in T_1. This cause is, however, less probable as no differences have been reported between eye tissues with long and short T_1-values in regard to the presence of paramagnetic substances.

In some cases the resonance signals suggest the presence of two components (Fig. 3), especially in the corpus vitreum and the cortical parts of the lens. Such a two-component signal has probably been observed earlier in other biologic substances such as human cervical mucus (ODEBLAD and BRYHN 1957). Two components may have been present also in others of our samples, but if so the shift in position has been insufficient to produce the asymmetric form of the signals necessary for detection of the two possible components. For comparison, a symmetric position,

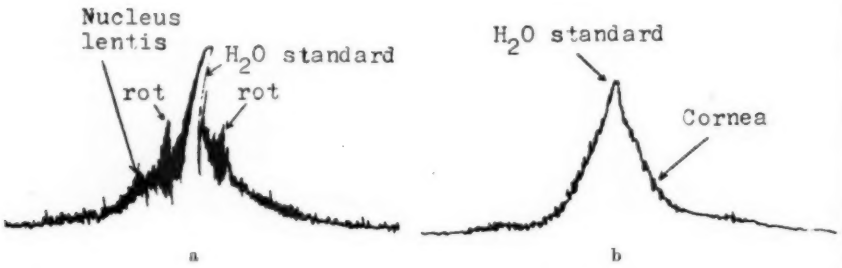

Fig. 4. a) Broad resonance peak of a lens nucleus with a water standard introduced (narrow peak) giving rise to rotation peaks. In this case no filtering was used so the noise is large. b) Sample from the cornea. More effective noise filtering than in (a).

when two components are present, is indicated in Fig. 4. The one component is a water reference signal introduced into the sample.

In such complex tissues as those of the eye the protons bound in — NH —, — CH_2 — and similar groups will give rise to resonance peaks located around + 3 and + 4 ppm from water. In tissues containing fat cells and in the optic nerve a peak of this nature was easy to identify, but in other tissues it is probably too broad or of too low intensity to be recognized. In any case the asymmetric component of low shift described above appears to be of a nature different from this last peak of high shift.

It was mentioned in the introduction that the amount of free water in the eye tissues varies considerably. It would be of great interest to be able to identify these components with the 'free' and with the protein-bound water in the tissues. Our investigations cannot answer this question definitely, but it is remarkable that those tissues which are supposed to have a large part of their water in the 'free' form show a narrow main signal and sometimes signs of a broad component. In those tissues, however, in which the amount of 'free' water is supposed to be lower, the narrow component could not be identified. The only and as yet unexplainable difference was observed for the optic nerve which has a distinct narrow main signal, but where the 'free' water according to FISCHER has the remarkably low value of only 26 %.

That in some tissues only one broad signal appears may, however, also be explained by an exchange between 'free' and protein-bound water provided this exchange is rapid enough. Further studies will be published elsewhere (HUGGERT and ODEBLAD 1959).

In those parts of the eye that have the highest water content the values of T_1 and T_2 are of similar magnitude but in the organs containing less water, T_2 appears to be about ten times smaller than T_1. As stated in

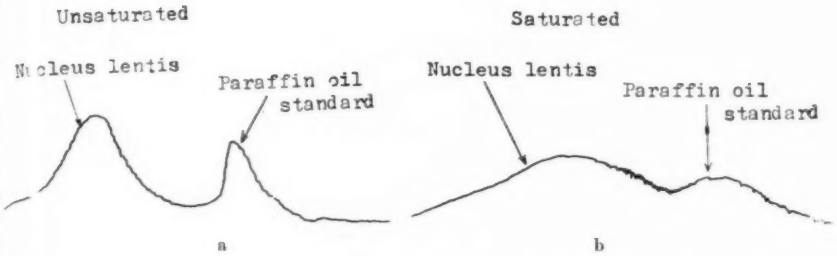

Fig. 3. a) Spectrum of lens nucleus sample with paraffin oil standard. Unsaturated condition. b) Same sample in saturated condition. The peaks are broader, but the surface ratio between the peaks is about the same as in (a). This indicates that T_1 is nearly equal for standard and sample or smaller for lens nucleus than for the paraffin oil used.

the beginning, in pure liquids T_1 and T_2 ought to be nearly equal, but in solids T_1 is much longer than T_2. Our results therefore indicate preliminarily that the water in the last mentioned organs may in part be involved in a more rigid structure than water in the 'free' state.

SUMMARY

The proton magnetic resonance signals and magnetic relaxation times of different parts of the eye have been recorded. Narrow resonance lines seemed to arise from tissues and fluids with a high water content, while a lower water percentage was associated with a broader signal. The results are discussed with special reference to the possibility of distinguishing between free and protein-bound water.

ZUSAMMENFASSUNG

Die protonmagnetischen Resonanzsignale und die magnetischen Relaxationszeiten verschiedener Abschnitte des Auges sind registriert worden. Enge Resonanzlinien scheinen von Geweben und Flüssigkeiten mit hohem Wassergehalt auszugehen, während ein geringerer prozentueller Wassergehalt mit breiteren Linien verknüpft war. Die Ergebnisse werden unter besonderer Bezugnahme auf die Möglichkeit, zwischen freiem und eiweissgebundenem Wasser unterscheiden zu können, besprochen.

RÉSUMÉ

Les auteurs ont enregistré les signaux de résonance magnétique des protons et les temps de relaxation magnétique de diverses parties de l'œil. Les lignes de résonance étroites semblent provenir des tissus et des liquides à forte teneur en eau, alors que la faible teneur en eau se traduit par des signaux plus larges. Les auteurs étudient ces résultats, en particulier en ce qui concerne la possibilité de distinguer l'eau libre et l'eau liée aux protéines.

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LIVER RESPIRATION IN NORMAL AND ROENTGEN IRRADIATED RATS

The utilisation of a succinate

by

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Previous papers from this laboratory (1, 2) have dealt with investigations upon cholesterol synthesis from acetates in the livers of rats and mice after whole body roentgen irradiation. The increase found in the endogeneous respiration of the liver (3) under the same experimental conditions seemed interesting in the light of our previous findings (1) that the same dose of roentgen irradiation produced an increase in the liver's cholesterol synthesis in vitro the first day after irradiation. We therefore decided to investigate the powers of oxidation of livers from non-irradiated and irradiated rats against different substrates.

The experiment now described was designed to study the in vitro respiration of rat liver slices from normal and irradiated animals with a succinate as substrate; 2,3-C^{14}-succinate was selected for the investigation and the oxygen uptake and the carbon dioxide production was measured.

Experimental. Male rats of the Wistar strain, 7 to 8 weeks of age and weighing 150 to 180 g, were used. The animals were reared on our standard diet, the composition of which was described in our previous paper (3). The radiation treatment consisted of a

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Table

The respiration of rat liver slices after whole body roentgen irradiation

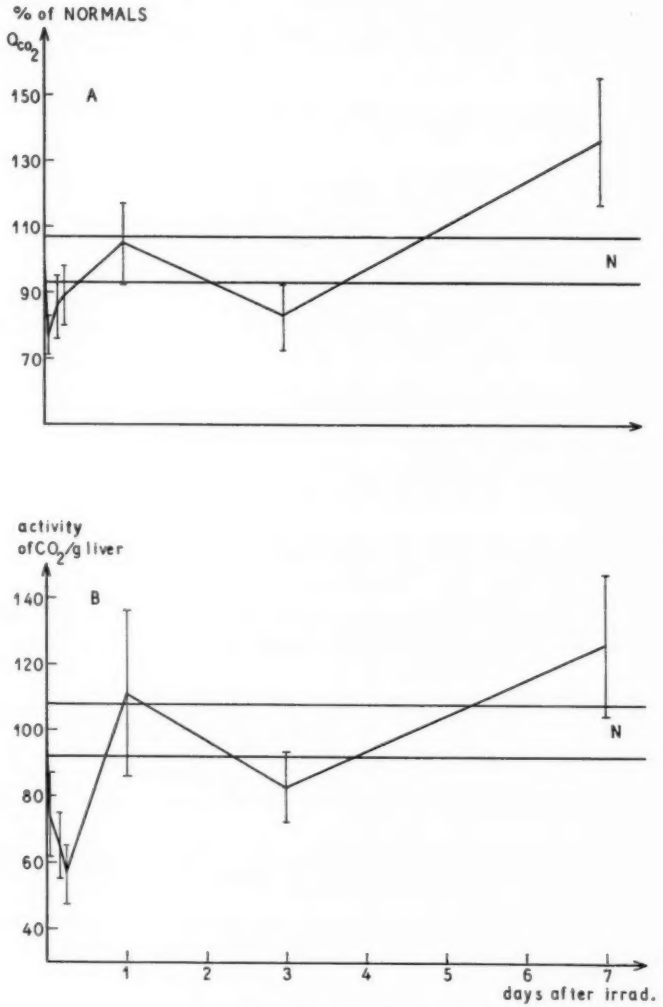
Exp.	No. of rats	mg $BaCO_3$ per mg dry tissue	Spec. act. cpm/mg $BaCO_3$	Total cpm per mg dry tissue	Q_{CO_2}	$-Q_{O_2}$	R.Q.	Time after irradiation
1	7	0.154±0.021	127±10	20.8±3.5	17.5±2.4	12.1±1.9	1.36±0.40	normals
2	4	0.119±0.008	129±12	15.4±2.6	13.5±0.3	12.8±2.5	1.05±0.26	1 hour
3	3	0.132±0.011	94±26	13.2±1.8	15.0±1.2	18.3±0.3	0.94±0.08	3.5 hours
4	3	0.137±0.011	87±8	11.9±1.9	15.6±1.2	12.1±2.3	1.34±0.27	6 hours
5	3	0.161±0.016	141±28	23.0±6.7	18.3±1.8	11.7±1.4	1.45±0.32	1 day
6	4	0.128±0.013	109±14	14.1±3.3	14.6±1.2	11.9±1.1	1.23±0.21	3 days
7	4	0.210±0.033	126±32	26.3±6.8	23.9±3.7	8.65±1.3	2.78±0.85	7 days

single dose of 450 r whole body roentgen irradiation (HVL 0.95 mm Cu, dose rate 40 r/min), the animals being restrained in perspex cages. The rats were killed at different time intervals (as shown in Table 1) by fracture of the neck and then decapitated for uniform exsanguination. The livers were removed as quickly as possible and kept in ice-cold, oxygen-saturated KREBS (4) phosphate buffer with a pH of 7.1.

Respiration measurement technique. The livers were sliced into sections 0.4 to 0.5 mm in thickness by means of a MCILWAIN (6) tissue slicer. For the measurement of oxygen uptake approximately 100 mg of slices were transferred to a Warburg flask with 3 ml of the phosphate buffer mentioned above, but which was in addition 0.02 molar with respect to sodium succinate. The central well of the Warburg flask was filled with 0.2 ml of 20 % potassium hydroxide, and the flask flushed with oxygen for 10 minutes; it was then fitted onto the Warburg apparatus. After 20 minutes equilibration at 37.5° C, readings were taken and repeated at 10 minute-intervals over a period. Apart from the details mentioned, the technique used with the Warburg apparatus was exactly the same as that described by UMBREIT (8). After the last reading, the slices were filtered off onto a sintered glass filter and dried to a constant weight at 105° C. In all determinations the oxygen uptake per milligram dry tissue was found to be proportional to the elapsed time up to at least the first hour, and the results were expressed as μl O_2 uptake per mg dry tissue per hour, the so-called Q_{O_2}.

The CO_2 production was measured under analogous experimental conditions, but a part of the succinate was labelled at the carbons 2 and 3 with C^{14}; the activity of the succinate in the buffer was 3 μc per 1 ml. The experiment was carried out in specially designed incubation flasks (1), which permitted an easy quantitative isolation of the produced carbon dioxide. The weight of liver slices in each experiment was about 1 g and the amount of phosphate buffer 15 ml. The carbon dioxide was absorbed in potassium hydroxide (20 %); to interrupt the reaction and to expel any dissolved CO_2 the buffer was acidified. When the absorption of the CO_2 was complete, the carbonate was precipitated in the usual way as $BaCO_3$ and the amount was determined by weighing. The Q_{CO_2} value was calculated from the amount of barium carbonate produced per hour per mg dry tissue by multiplication by the factor 113.7 to give the μl CO_2 under standard conditions.

A known amount of the $BaCO_3$ was plated on a standard aluminium dish for radioac ivity measurement on a flow counter. Corrections were made for dead time, backgr und, efficiency and self-absorption; in the last case the specific activity was calculated fo a 15 mg/cm² standard sample from an experimental self-absorption curve.



Diagrams showing CO_2 production in rat liver slices (top diagram) and the utilization of 2,3-C^{14} succinate for $C^{14}O_2$ production (the lower diagram), both as a function of time after whole body roentgen irradiation.

Results and Discussion

The oxygen uptake reached a maximum 3.5 hours after irradiation as compared with unirradiated animals, and fell below normal towards the seventh day after irradiation as shown in the table on p. 394.

A decreasing response to a succinate by liver tissue was found by ROSKELLEY et coll. (7) when Wistar rats were given carcinogens such as p-dimethylaminoazobenzene (butter yellow) about 100 days before the animals developed the first tumours.

Whereas the oxygen uptake of normal tissue slices increased up to 250 % in the presence of a succinate, tumour slices failed to respond, or responded very little, as shown by MAYER (5) with hepatoma produced in Wistar rats by p-dimethylaminoazobenzene.

It seems likely to us that the roentgen irradiation of the rats produced a similar metabolic defect as carcinogens in the utilization of a succinate.

The total amount of CO_2 produced fell to about 75 per cent of normal 1 hour after irradiation, and was significantly increased 7 days after irradiation, as compared with normal.

The radioactivity of the expired CO_2 per mg dry liver tissue follows the curve for the production of the total CO_2 as shown in the upper of the two diagrams, which indicates that the utilization of succinate changes to the same extent as the production of CO_2 from the liver's own resources (lower diagram). As may be seen from the table, the specific activity of the produced $BaCO_3$ in cpm/mg did not vary much. The specific activity of the expired CO_2, measured as $BaCO_3$, was about a quarter of that of the incubated succinate, measured as $BaCO_3$, which indicates that the succinate was not the only substrate used for CO_2 production. The specific activity of the 2,3-C^{14} succinate, measured as $BaCO_3$, under the same conditions, was 597 ± 26 cpm/mg $BaCO_3$.

The calculated respiratory quotients of normal and irradiated rats are given in the table. If the succinate were the only substrate metabolized to CO_2, the R. Q. should be 1 as we found in normal animals. The R. Q. remained at this value until the third day after irradiation. This together with the lowered specific activity of the succinate, indicates that an endogenous substrate of a carbohydrate type was metabolized.

The seventh day after irradiation the R. Q. was significantly over 2. this being due to both an elevation of the CO_2 production and a fall in the O_2 utilization as compared with normal rats. The elevation of the R. Q. over 1 might have been caused by a conversion of carbohydrate or of the substrate succinate to fat.

SUMMARY

The oxygen uptake and CO_2 production in liver slices from normal and whole body roentgen irradiated rats (450 r) with succinate as substrate has been investigated. It appeared that roentgen irradiation of the rats produced a similar metabolic defect in the utilization of succinate as carcinogens.

ZUSAMMENFASSUNG

Die Sauerstoffaufnahme und die Kohlendioxidproduktion in Leberschnitten normaler und totalbestrahlter Ratten (450 r) in einem Succinatsubstrat ist untersucht worden. Es hat den Anschein, dass die Röntgenbestrahlung der Ratten einen gleichartigen metabolischen Defekt bei der Anwendung eines Succinates wie Karzinogene erzeugte.

RÉSUMÉ

Les auteurs ont étudié la consommation d'oxygène et la production de CO_2 par des tranches de foie provenant de rats normaux et de rats ayant subi une irradiation roentgen de tout le corps (450 r), placées dans un milieu contenant un succinate. Ils ont constaté que l'irradiation roentgen des rats cause un trouble métabolique de l'utilisation du succinate analogue à celui que produisent les agents carcinogènes.

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BOOK REVIEWS

PERCUTANEOUS SELECTIVE ANGIOGRAPHY OF THE COELIAC ARTERY. By Per Ödman. 168 pages, 95 illustrations and 14 tables. Acta radiol. (1958) Suppl. No. 159. Sw. Kr. 35: —.

The work describes the technique for percutaneous transfemoral selective angiography with injection of the contrast solution into the coeliac artery through a premodelled radiopaque polythene catheter. An amount of 0.7 to 1.1 ml of contrast medium per kg of body weight is injected at a speed of 10 to 12 ml per second. The various sections of the coeliac vascular system are studied by means of multiple exposures with a biplane film unit. Not only the coeliac artery and its branches but organs supplied by it, such as the spleen, liver, pancreas, and gastric mucous membrane, as well as veins from these organs are shown in the films. The possibilities and limitations of the method are illustrated from the results of 61 angiographic examinations. Other angiographic methods capable of reproducing the coeliac vascular system are also discussed, as well as their relative advantages and disadvantages as compared with percutaneous selective angiography of the coeliac artery.

The examinations considered normal in this work (control series) are used to throw light on the typical coeliac vascular system. The arteries and upper abdominal organs are given particular attention. Certain measurements were also made from the angiograms with a view to obtaining objective information regarding the dimensions, directions, and relations to the vertebral column of the different vessels.

The pathologic cases are assessed from the information obtained from the control series.

In cirrhosis of the liver, there were changes in both the hepatic and the splenic arterial systems. The spleen seems to hold large amounts of blood in these cases. In cancer of the stomach, the size and thickness of the tumour could be estimated when the conditions for examination were favourable. Intrahepatic neoplasms could be directly observed as defects in the contrast density in the liver and displacement and/or deformation of the intrahepatic arteries. Expansive processes in the pancreas could be directly observed by displacements of peri- or intrapancreatic arteries and/or defects in the contrast density in the organ. Inflammatory processes appeared as enlargement of the pancreas and local dilatation of the intra- and peripancreatic arteries.

The tolerance of the coeliac vascular system to contrast medium (Urografin, Schering) was tested in rabbits and dogs. After selective coeliac angiography the animals were sacrificed at varying intervals. The abdominal organs in contact with the contrast medium were examined macro- and microscopically. In addition, the liver function of the dogs was examined by the bromsulphalein method. These animal experiments demonstrated that Urografin in doses and concentrations corresponding to those used in coeliac angiography in man has no deleterious effects in rabbits, and rarely in dogs, and that such effects, if any, are reversible.

Autoreview

Der Lungenboeck im Röntgenbild. Von K. Wurm, H. Reindell und L. Heilmeyer, 220 S., 180 Abb. George Thieme, Stuttgart 1958. DM 78:—.

The very fact that this book is based on a series of 400 cases — probably the largest material hitherto investigated — is sufficient to make it of great interest.

The authors begin by discussing how the disease should be defined and come to the conclusion that it is not possible to suggest any satisfactory definition so long as nothing is known regarding the etiology and pathogenesis. Previous attempts have been unsuccessful. This difficulty is also reflected in the names given to the condition: lupus pernio, miliary lupoid, sarcoidosis, and lymphogranulomatosis benigna. All these names suffer from the disadvantage that they are not comprehensive enough to cover the entire clinical entity; some of them are even misleading. The disease is usually named after authors who either described it at an early date or who have studied it in some detail. There is no internationally acknowledged name. The authors of this book chose the name Boeck's disease because it is short and convenient, and is the term most widely used in Germany. They point out, however, that the condition might just as well have been referred to as Besnier's or Schaumann's disease. It was Schaumann who demonstrated that it is a generalized systemic disease in the mesenchymal tissues producing in the main marked signs referable to the lymphatic system.

The material discussed in the book consists for the most part of chronic cases, but a few acute ones are also included. The clinical symptomatology is described briefly but at sufficient length.

The authors divide the disease into 3 stages based on the roentgen appearances. They report that in Stage I enlarged lymph nodes in the hilus of the lung and in the mediastinum are all that are to be seen. The condition had progressed to Stage II in 60 to 70 per cent of their cases. In this stage, small infiltrations appear in the lungs; at the same time a decrease in the lymph nodes in the mediastinum occurs. As Stage II advances it is often not possible to distinguish any enlarged lymph nodes; this may cause difficulties in the differential diagnosis. Stage II has been divided into five groups and a distinction made between a lymphogenic and haematogenic distribution; no clear evidence is given to show why the distribution should be lymphogenic in some cases and haematogenic in others, and the justification for introducing five groups is not convincing. In the opinion of the reviewer, however, it would seem to be correct to make a distinction between cases with small, miliary parenchymal infiltrations and those with large ones of 3 to 5 mm diameter, seeing that, in Nitter's material, the latter had a definitely poorer prognosis. In Stage III, large conglomerates are distinguishable (III a), and finally (III b) fibrosis and shrinking occurs.

The course of the disease is described in detail. According to these authors, it is so characteristic, and conforms so regularly to type, that an unequivocal diagnosis can be made if a series of roentgenograms taken over a fairly long period is available. On the other hand, a roentgenogram from one isolated examination is not pathognomonic at any stage.

About 150 of the 220 pages in the book consist of an atlas of good reproductions of typical roentgenograms. Only 2 of the 176 films of the lungs are lateral views, however. It would almost seem as if the authors underestimate the value of the lateral view. This projection would have been of considerable assistance in several of the cases. This criticism is particularly applicable in the section on the differential diagnosis between silicosis and Stage III. The chapter on the differential diagnosis is otherwise most instructive.

Our knowledge regarding the prognosis in Boeck-Schaumann disease has previously been deficient, and the half page devoted to this aspect is extremely valuable. The outlook is best in cases with an acute onset and a relatively short course; the more protracted

the course the more hopeless is the prognosis. The prospects of recovery are more promising in women than in men. Death may occur, even in Stage II, from wide-spread infiltration in the pulmonary parenchyma and respiratory insufficiency; this is uncommon, however. In Stage III, severe fibrosis and shrinking develop, ending in cor pulmonale and death either as a result of respiratory or of cardiac insufficiency. The authors estimate the proportion of recoveries in Stage I to be 30 per cent and in Stage II a further 40 to 50 per cent. The remaining 20 to 30 per cent progress to Stage III, which always involves invalidism or premature death.

Reference to the literature is made here and there in the text, but the work lacks a complete list of references. This is a disadvantage. In other respects the book is well written and pleasant to read. It is warmly recommended.

Gunnar Jönsson

GUIDE TECHNIQUE ET TOPOGRAPHIQUE D'EXPLORATION BRONCHOLOGIQUE (Bronchoscopie et bronchographie). Par Jean Ioannou en collaboration avec L. Duchet-Suchaux et A. Pinelli. 114 pages, 66 figures. Masson, Paris 1956. 1,400 fr.

"Simple guide technique et topographique. Son seul but est didactique." These are the words which unassumingly introduce this small, well-written, and easily read book. The author appears to be a specialist in bronchoscopy and bronchography: he, however, is not a radiologist, and this to some extent affects the presentation. And so in turn a reader without radiologic experience must be not a little confused when he is assured that to achieve success a large number of films is necessary although sometimes only one and often one of the last determines the interpretation.

In certain cases the writer has used tomobronchography in the successful demonstration of changes not revealed by conventional bronchography. As this is an elementary book, it should have been pointed out that simultaneous bilateral bronchography should not generally be performed even if the employment of tomography overcomes the superimposition of the right and left lung fields in the conventional lateral views. The topography and anatomical variations of the bronchi are reviewed and illustrated with numerous schematic drawings. The films vary somewhat in quality; the majority are good.

Uno A. T. Norlin

SONDERAUSSCHUSS RADIOAKTIVITÄT Bundesrepublik Deutschland. Erster Bericht Januar 1958. 68 S., 5 Abb., 2 Karten. Georg Thieme. Stuttgart 1958. DM 4.30.

This booklet gives a preliminary report on methods and measuring results, mainly for the period from October 1956 to October 1957 inclusive, on radioactive contamination of rain, ground, vegetation, foodstuffs etc. in the German Federal Republic. The bearing of radiation on public health and a future research program on doses from various sources are briefly discussed.

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